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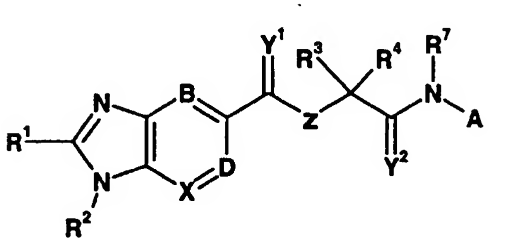

(I)

(57) Abstract: An isomer, enantiomer, diastereoisomer, or tautomer of a compound, represented by formula (I): wherein R^1 is selected from: H, haloalkyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{2-6})alkynyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl, Het all optionally substituted; R2 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{6-10})bicycloalkyl, 6- or 10-membered aryl, or Het all optionally substituted; B is N or CR^5, wherein R^5 is H, halogen, haloalkyl, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; X is N or CR^5; D is N or CR^5; each of Y_1 and Y_2 is independently O or S; Z is O, N, or NR^z wherein R^z is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; R^3 and R^4 are each independently H, (C_{1-6})alkyl, first (C_{3-7})cycloalkyl, 6- or 10-membered aryl, Het (C_{1-6})alkyl-6- or 10-membered aryl, (C_{1-6})alkyl-Het; or each R^3 and R^4 are independently covalently bonded together to form second (C_{3-7})cycloalkyl, or heterocycle, all optionally substituted; or when Z is N, either R^3 or R^4 are independently covalently bonded thereto to form a nitrogen-containing heterocycle; R^7 is H, $(C_{1-6}$ alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or R^7 is covalently bonded to either of R^3 or R^4 to form a heterocycle; A is (C_{1-6}) alkyl-CONHR^8 wherein R^8 is-6- or 10-membered aryl, or Het; or A is a 6- or 10-membered aryl, or Het said aryl or Het being optionally substituted; or a salt or a derivative thereof; such compounds being potent inhibitors of HCV NS5B polymerase.

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VIRAL POLYMERASE INHIBITORS

Technical field of the invention

The invention relates to inhibitors of RNA dependent RNA polymerases, particularly those viral polymerases within the Flaviviridae family, more particularly HCV polymerase.

Background of the Invention

About 30,000 new cases of hepatitis C virus (HCV) infection are estimated to occur in the United States each year (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051). HCV is not easily cleared by the hosts' immunological defences; as many as 85% of the people infected with HCV become chronically infected. Many of these persistent infections result in chronic liver disease, including cirrhosis and hepatocellular carcinoma (Hoofnagle, J.H.; 1997; *Hepatology* **26**: 15S-20S). There are an estimated 170 million HCV carriers world-wide, and HCV-associated end-stage liver disease is now the leading cause of liver transplantation. In the United States alone, hepatitis C is responsible for 8,000 to 10,000 deaths annually. Without effective intervention, the number is expected to triple in the next 10 to 20 years. There is no vaccine to prevent HCV infection. Prolonged treatment of chronically infected patients with interferon or interferon and ribavirin is the only currently approved therapy, but it achieves a sustained response in fewer than 50% of cases (Lindsay, K.L.; 1997; *Hepatology* **26**: 71S-77S, and Reichard, O.; Schvarcz, R.; Weiland, O.; 1997 *Hepatology* **26**: 108S-111S).

HCV belongs to the family *Flaviviridae*, genus *hepacivirus*, which comprises three genera of small enveloped positive-strand RNA viruses (Rice, C.M.; 1996; "*Flaviviridae*: the viruses and their replication"; pp. 931-960 in *Fields Virology*; Fields, B.N.; Knipe, D.M.; Howley, P.M. (eds.); Lippincott-Raven Publishers, Philadelphia Pa.). The 9.6 kb genome of HCV consists of a long open reading frame (ORF) flanked by 5' and 3' non-translated regions (NTR's). The HCV 5' NTR is 341 nucleotides in length and functions as an internal ribosome entry site for cap-independent translation initiation (Lemon, S.H.; Honda, M.; 1997; *Semin. Virol.* **8**:

274-288). The HCV polyprotein is cleaved co- and post-translationally into at least 10 individual polypeptides (Reed, K.E.; Rice, C.M.; 1999; *Curr. Top. Microlbiol. Immunol.* **242**: 55-84. The structural proteins result from signal peptidase induced cleavage in the N-terminal portion of the polyprotein. Two viral proteases mediate downstream cleavages to produce non-structural (NS) proteins that function as components of the HCV RNA replicase. The NS2-3 protease spans the C-terminal half of the NS2 and the N-terminal one-third of NS3 and catalyses *cis* cleavage of the NS2/3 site. The same portion of NS3 also encodes the catalytic domain of the NS3-4A serine protease that cleaves at four downstream sites. The C-terminal two-thirds of NS3 is highly conserved amongst HCV isolates, with RNA-binding, RNA-stimulated NTPase, and RNA unwinding activities. Although NS4B and the NS5A phosphoprotein are also likely components of the replicase, their specific roles are unknown. The C-terminal polyprotein cleavage product, NS5B, is the elongation subunit of the HCV replicase possessing RNA-dependent RNA polymerase (RdRp) activity (Behrens, S.E.; Tomei, L.; DeFrancesco, R.; 1996; *EMBO J.* **15**: 12-22; and Lohmann, V.; Kömer, F.; Herian, U.; Bartenschlager, R.; 1997; *J. Virol.* **71**: 8416-8428). It has been recently demonstrated that mutations destroying NS5B activity abolish infectivity of RNA in a chimp model (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051).

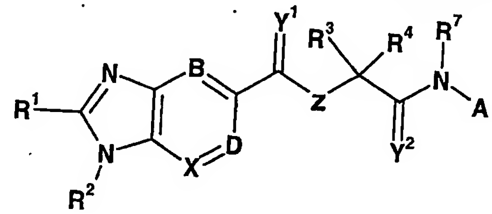
The development of new and specific anti-HCV treatments is a high priority, and virus-specific functions essential for replication are the most attractive targets for drug development. The absence of RNA dependent RNA polymerases in mammals, and the fact that this enzyme appears to be essential to viral replication, would suggest that the NS5B polymerase is an ideal target for anti-HCV therapeutics. WO 00/06529 reports inhibitors of NS5B which are α, γ-diketoacids.
WO 00/13708, WO 00/10573, WO 00/18231, and WO 01/47883 report inhibitors of NS5B proposed for treatment of HCV.

SUMMARY OF THE INVENTION

It is therefore an object of the invention to provide a novel series of compounds having improved inhibitory activity against HCV polymerase.

In a first aspect of the invention, there is provided an isomer, enantiomer,

diastereoisomer, or tautomer of a compound, represented by formula I:



wherein (I)

R^1 is selected from: R^{11}, OR^{11}, SR^{11}, $COOR^{11}$, $SO_2N(R^{12})_2$, $N(R^{12})_2$, , $CON(R^{12})_2$, $NR^{12}C(O)R^{12}$ or $NR^{12}C(O)NR^{12}$ wherein R^{11} and each R^{12} is independently H, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{2-6})alkynyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, said R^{11} and R^{12} being optionally substituted with R^{10}; or both R^{12} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

R^2 is selected from (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**,

said alkyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, **Het**, alkyl-aryl and alkyl-**Het** being optionally substituted with from 1 to 4 substituents selected from: halogen, or

a) (C_{1-6})alkyl optionally substituted with:

- OR^{21} or SR^{21} wherein R^{21} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or

- $N(R^{22})_2$ wherein each R^{22} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{22} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

b) OR^{23} wherein R^{23} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**;

c) SR^{24} wherein R^{24} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; and

d) $N(R^{25})_2$ wherein each R^{25} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{25} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

B is N or CR^5, wherein R^5 is H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or R^5 is OR^{51} or SR^{51}, COR^{51} or $NR^{51}COR^{51}$ wherein each R^{51} is independently H, (C_{1-6})alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or R^5 is $NR^{52}R^{53}$ wherein R^{52} and R^{53} are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or both R^{52} and R^{53} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

X is N or CR^5, wherein R^5 is as defined above;

D is N or CR^5, wherein R^5 is as defined above;

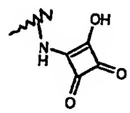
each of Y_1 and Y_2 is independently O or S;

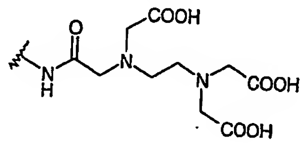
Z is O, N, or NR^6 wherein R^6 is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

R^3 and R^4 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** are optionally substituted with R^{30}; or R^7 and R^8 are covalently bonded together to form second (C_{3-7})cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when **Z** is NR^6, either of R^7 or R^8 is covalently bonded to R^6 to form a nitrogen-containing 5-or 6-membered heterocycle;

R^7 is H, $(C_{1-6}$ alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**, all of which optionally substituted with R^{70}; or R^7 is covalently bonded to either of R^3 or R^4 to form a 5- or 6-membered heterocycle;

A is a 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, (C_{1-6}) alkyl-CONH-aryl or (C_{1-6}) alkyl-CONH-**Het**, all of which being optionally substituted with:



, 

, or $\mathbf{R}^{100}$;

or a salt or a derivative thereof;

wherein **Het** is defined as:

5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicycle having 1 to 5 heteroatoms selected from O, N and S; and

$\mathbf{R}^{10}$, $\mathbf{R}^{30}$, $\mathbf{R}^{70}$ and $\mathbf{R}^{100}$ are defined as:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or

- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R}^{150}$;

b) OR^{104} wherein $\mathbf{R}^{104}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R}^{150}$;

c) $OCOR^{105}$ wherein $\mathbf{R}^{105}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R}^{150}$;

d) SR^{108}, $SO_2N(\mathbf{R}^{108})_2$ or $SO_2N(\mathbf{R}^{108})C(O)\mathbf{R}^{108}$ wherein each $\mathbf{R}^{108}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R}^{108}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with

R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};
or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl,

aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}; and

wherein R^{150} is defined as:

1 to 3 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or

heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160}, or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-

cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with **R**^{160};

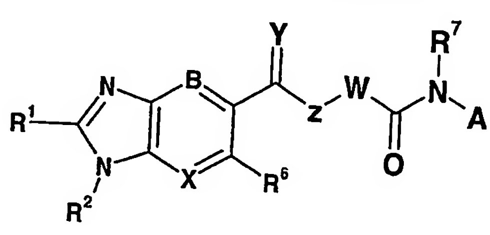
i) COR^{127} wherein **R**^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with **R**^{160};

j) tetrazole, COOR^{128} wherein **R**^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with **R**^{160}; and

k) CONR^{129}R^{130} wherein **R**^{129} and **R**^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both **R**^{129} and **R**^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with **R**^{160};

wherein **R**^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, COOR^{161}, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, N(R^{162})$_2$, SO_2N(R^{162})$_2$, NR^{162}COR^{162} or CON(R^{162})$_2$, wherein **R**^{161} and each **R**^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both **R**^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle,

Alternatively, there is provided a compound of formula Ia :



Ia

wherein $\mathbf{R^1}$ is selected from: 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S and phenyl, said heterocycle and phenyl being optionally substituted with from 1 to 4 (C_{1-4})alkyl substituents;

$\mathbf{R^2}$ is selected from: (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-3})alkyl, and norbornane;

X is CH or N;

$\mathbf{R^6}$ is H or $(C_{1-6}$ alkyl);

Y is O or S;

B is N or $\mathbf{CR^5}$, wherein $\mathbf{R^5}$ is H or (C_{1-6}) alkyl with the proviso that **X** and **B** are not both N;

Z is O, N, or NH;

W is $\mathbf{CR^3R^4}$ wherein $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently H, $(C_{1-6}$ alkyl), $(C_{3-7}$ cycloalkyl), $(C_{1-6}$ alkyl)phenyl, $(C_{1-6}$ alkyl)-$(C_{3-7}$ cycloalkyl), $(C_{3-7}$ cycloalkyl)-(C_{1-6} alkyl), $(C_{3-7}$ cycloalkyl)-$(C_{2-4}$ alkenyl), $(C_{1-6}$ alkyl)-OH, phenyl, CH_2biphenyl, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S, $(C_{1-6}$ alkyl)-5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, or $(C_{1-6}$ alkyl)-9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S, or $\mathbf{R^3}$ and $\mathbf{R^4}$ are covalently bonded together to form $(C_{3-7}$ cycloalkyl), 4-, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S; or when **Z** is N, either $\mathbf{R^3}$ or $\mathbf{R^4}$ is covalently bonded thereto to form a 5-membered heterocycle;

> wherein said alkyl, cycloalkyl, heterocycle, heterobicycle, phenyl are optionally substituted with from 1 to 4 substituents selected from: OH, COOH, $(C_{1-6}$ alkyl), $(C_{2-4}$ alkenyl), $CONH_2$, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, NHCOCOOH, NHCOCON$(C_{1-6}$ alkyl$)_2$, NHCOCONH$(C_{1-6}$ alkyl), SH, $S(C_{1-6}$ alkyl), $NHC(=NH)NH_2$, and COO$(C_{1-6}$alkyl);

$\mathbf{R^7}$ is H or $(C_{1-6}$ alkyl);

A is selected from: $(C_{1-3}$alkyl)CONHaryl, 6- or 10-membered aryl, biphenyl, 5- or 6-atom heterocycle having 1 to 4 heteroatoms selected from O, N and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

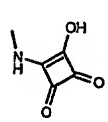
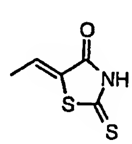
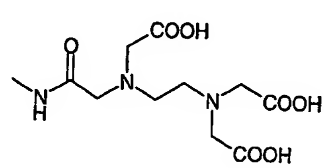
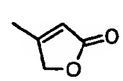
wherein said aryl, biphenyl, first heterocycle, and heterobicycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, COO(C_{1-6})alkyl, (C_{1-6})alkyl, (C_{1-6})alkylCOOH, $(C_{1-6}$ alkyl$)(C_{2-4}$ alkynyl), (C_{1-6})alkyl-hydroxy, phenyl, benzyloxy, halogen, (C_{2-4})alkenyl, (C_{2-4})alkenyl-(C_{1-6})alkyl-COOH, 5- or 6-membered second heterocycle having 1 to 4 heteroatoms selected from O, N and S, NH-5- or 6- membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S,

wherein said second heterocycle and phenyl being optionally substituted with from 1 to 4 substituents selected from: $(C_{1-6}$ alkyl), CF_3, OH, $(C_{1-6}$alkyl) COOH, O$(C_{1-6}$alkyl)COOH, $(C_{1-6}$alkyl) COO$(C_{1-6}$alkyl), CH_2phenyl, COO$(C_{1-6}$ alkyl), $(C_{1-6}$alkyl)O$(C_{1-6}$alkyl), COOH, NCH$(C_{1-6}$alkyl$)_2$, NCO$(C_{1-6}$ alkyl), NH_2, NH$(C_{1-6}$ alkyl), and N$(C_{1-6}$ alkyl$)_2$;

halogen, OPO_3H, benzyl, sulfonamido, SH, $SOCH_3$, SO_3H, SO_2CH_3, S$(C_{1-6}$ alkyl)COOH, -$CONH_2$, -$COCH_3$, (C_{1-3})alkyl, $(C_{2-4}$alkenyl)COOH

wherein said alkenyl is optionally substituted with from 1 to 2 $(C_{1-6}$ alkyl) substituents,

$(C_{2-4}$alkenyl)COO$(C_{1-6}$alkyl), tetrazolyl, COOH, triazolyl, OH, NO_2, NH_2, -O$(CH_2)_p$COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, (C_{1-4})alkoxy$(C_{1-6}$ alkyl)COOH, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, -NHCOCOOH, -NHCOCONHOH,-$NHCOCONH_2$, -$NHCOCONHCH_3$, -NHCO(C_{1-6})alkyl-COOH, -NHCOCONH(C_{1-6})alkyl-COOH, -NHCO(C_{3-7})cycloalkyl-COOH, -NHCONH(C_{6-10})aryl-COOH, - NHCONH(C_{6-10})aryl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-COOH,- NHCONH(C_{1-6})alkyl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-(C_{2-6})alkenyl-COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-O(C_{1-6})alkyl COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-COOH, -$NHCH_2COOH$, -$NHCONH_2$, -NHCO(C_{1-6})hydroxyalkyl COOH, -OCO(C_{1-6})hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,

 ,  ,  ,  , -NHCN, -NHCHO, -$NHSO_2CH_3$, -$NHSO_2CF_3$, coumarin, (C_{1-6})alkyl-amino, di-(C_{1-6})alkyl-amino, C(halogen$)_3$, -NH(C_{2-4})acyl, -NH(C_{6-10})aroyl,

-CONH(C_{1-6}alkyl), -CO(C_{1-6})alkyl-COOH, -CONH(C_{1-6})alkyl-COOH, -CO-NH-alanyl, -CONH(C_{2-4})alkylN(C_{1-6}alkyl)$_2$, -CONH(C_{2-4}) alkyl-**Het** -CONH(C_{2-4}) alkyl-(COOH)-**Het** -CONH(C_{1-2} alkyl) (OH)(C_{1-2} alkyl) OH, -CONH(C_{1-6}) alkyl-COOH, -CONH(C_{6-10} aryl), -CONH-**Het** -CONH(C_{6-10}) aryl-COOH, -CONH(C_{6-10}) aryl-COO(C_{1-6}) alkyl, -CONH(C_{1-6}) alkyl-COO(C_{1-6}) alkyl, -CONH(C_{6-10}) aryl-(C_{1-6})alkyl-COOH, -CONH(C_{6-10}) aryl-(C_{2-6})alkenyl-COOH,

or salt thereof.

In a second aspect of the invention, there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, as an inhibitor of RNA dependent RNA polymerase activity of the enzyme NS5B, encoded by HCV.

In a third aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as an inhibitor of HCV replication.

In a fourth aspect of the invention, there is provided a method of treating or preventing HCV infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In a fifth aspect of the invention, there is provided a pharmaceutical composition for the treatment or prevention of HCV infection, comprising an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a sixth aspect of the invention, there is provided a method of treating or preventing HCV infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in combination with another anti-HCV agent.

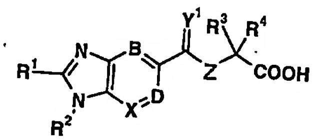
In a seventh aspect of the invention, there is provided a use of a compound of formula I, for the manufacture of a medicament for the treatment of HCV infection.

In a eighth aspect of the invention, there is provided a use of a compound of formula

I, to prevent HCV infection.

In an ninth aspect of the invention, there is provided a use of a compound of formula I, as an HCV polymerase inhibitor.

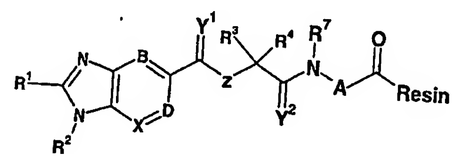
In an tenth aspect of the invention, there is provided an intermediate compound of formula (i):



(i)

wherein **R¹**, **R²**, **R³**, **R⁴**, **B**, **D**, **X**, **Y¹**, and **Z** are as defined herein, or a derivative thereof.

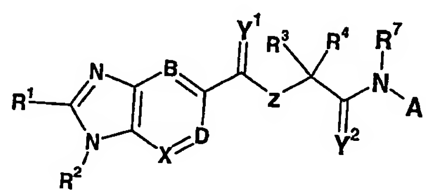
In a eleventh aspect of the invention, there is provided an intermediate compound of formula I(ii):



I(ii)

wherein **R¹**, **R²**, **R³**, **R⁴**, **R⁷**, **A**, **B**, **D**, **X**, **Y¹**, **Y²** and **Z** are as defined herein, or a derivative thereof.

In a twelfth aspect of the invention, there is provided a process for producing compounds of formula I,

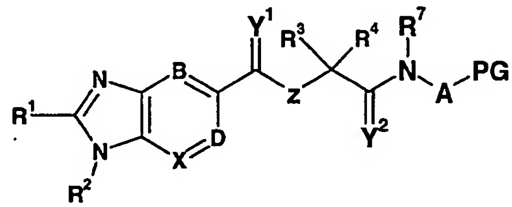


I

wherein **R¹**, **R²**, **R³**, **R⁴**, **R⁷**, **A**, **B**, **D**, **X**, **Y¹**, **Y²** and **Z** are as defined herein, comprising:

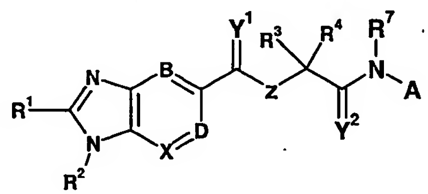
a) removing, in a mixture of an aqueous base or an aqueous acid in a co-

solvent, the protecting group (PG) from:



wherein R^1, R^2, R^3, R^4, R^7, **A**, **B**, **D**, **X**, Y^1, Y^2 and **Z** are as defined herein, and wherein **PG** is a carboxylic acid protecting group, so as to produce compounds of formula I.

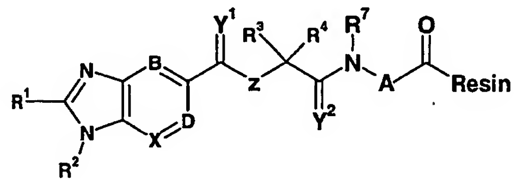
In a thirteenth aspect of the invention, there is provided a process for producing compounds of formula I,



I

wherein R^1, R^2, R^3, R^4, R^7, **A**, **B**, **D**, **X**, Y^1, Y^2 and **Z** are as defined herein, comprising:

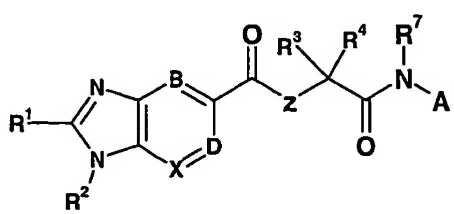
a) cleaving, under acidic conditions, intermediate compound I(ii)



I(ii)

so as to produce compounds of formula I, where R^1, R^2, R^3, R^4, R^7, **A**, **B**, **D**, **X**, Y^1 and Y^2 are as defined herein.

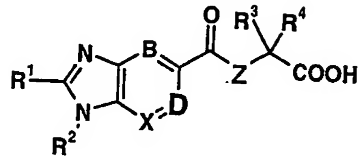
In a fourteenth aspect of the invention, there is provided a process for producing compounds of formula I,



I

wherein **R^1**, **R^2**, **R^3**, **R^4**, **R^7**, **A**, **B**, **D**, **X** and **Z** are as defined herein, comprising:

i) coupling intermediate compound of formula (i):



(i)

wherein **R^1**, **R^2**, **R^3**, **R^4**, **B**, **D**, **X**, and **Z** are as defined herein, or a derivative thereof, with **HN(R^7)-A** wherein **R^7** and **A** are as defined herein, to produce compound of formula **I**.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The following definitions apply unless otherwise noted:

As used herein, the terms "(C_{1-3}) alkyl", "(C_{1-4}) alkyl" or "(C_{1-6}) alkyl", either alone or in combination with another radical, are intended to mean acyclic straight or branched chain alkyl radicals containing up to three, four and six carbon atoms respectively. Examples of such radicals include methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl.

As used herein, the term "(C_{2-6}) alkenyl", either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight chain radical containing two to six carbon atoms.

As used herein, the term (C_{2-6}) alkynyl" either alone or in combination with another group, is intended to mean an unsaturated, acyclic straight chain sp hybridized radical containing 2 to six carbon atoms.

As used herein. the term "(C_{3-7}) cycloalkyl", either alone or in combination with another radical, means a cycloalkyl radical containing from three to seven carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term "(C_{5-7})cycloalkenyl", either alone or in combination with another radical, means an unsaturated cyclic radical containing five to seven carbon atoms.

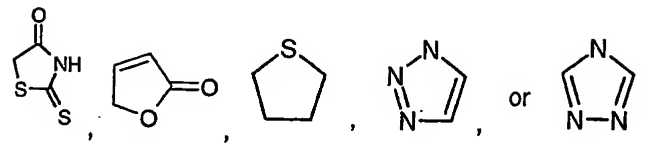
As used herein, the term "carboxy protecting group" defines protecting groups that can be used during coupling and are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), the disclosures of which are hereby incorporated by reference.

The α-carboxyl group of the C-terminal residue is usually protected as an ester (CPG) that can be cleaved to give the carboxylic acid. Protecting groups that can be used include: 1) alkyl esters such as methyl, trimethylsilylethyl and *t*-butyl, 2) aralkyl esters such as benzyl and substituted benzyl, or 3) esters that can be cleaved by mild base treatment or mild reductive means such as trichloroethyl and phenacyl esters.

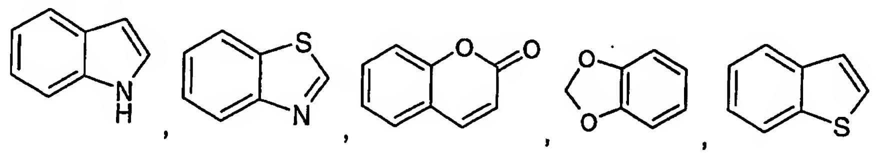
As used herein, the term "aryl", or "6- or 10-membered aryl" either alone or in combination with another radical means aromatic radical containing six or ten carbon atoms, for example phenyl or naphthyl.

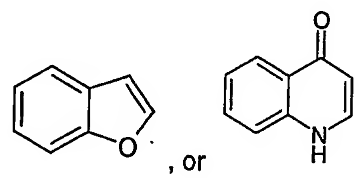
As used herein the term heteroatom means O, S or N.

As used herein, the term "heterocycle", either alone or in combination with another radical, means a monovalent radical derived by removal of a hydrogen from a five-, six-, or seven-membered saturated or unsaturated (including aromatic) heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur. Furthermore, "heterobicyclic" as used herein, means a heterocycle as defined above fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterocycles include, but are not limited to, pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, thiophene, coumarin, hydantoin, diazepine, 1H-imidazole, isoxazole, thiazole, tetrazole, piperidine, 1,4-dioxane, 4-morpholine, pyridine, pyridine-N-oxide, pyrimidine, thiazolo[4,5-b]-pyridine, quinoline, or indole, or the following heterocycles:



As used herein, the term "9- or 10-membered heterobicycle" or "heterobicycle" either alone or in combination with another radical, means a heterocycle as defined above fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterobicycles include, but are not limited to, thiazolo[4,5-b]-pyridine, quinoline, or indole, or the following:





As used herein, the term "**Het**" defines a 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicycle having 1 to 5 heteroatoms wherever possible, selected from O, N and S.

As used herein, the term "halo" means a halogen atom and includes fluorine, chlorine, bromine and iodine.

As used herein, the term "haloalkyl" is intended to mean an alkyl that is described above in which each hydrogen atom may be successively replaced by a halogen atom, for example CH_2Br or CF_3.

As used herein, the term "metal halide" is intended to mean any metal that is bonded to a halogen atom for use in a metal-catalyzed cross-coupling reaction. Examples of such metal halides include, but are not limited to, -MgCl, -CuCl, or -ZnCl and the like.

As used herein, the term "OH" refers to a hydroxyl group. It is well known to one skilled in the art that hydroxyl groups may be substituted by functional group

equivalents. Examples of such functional group equivalents that are contemplated by this invention include, but are not limited to, ethers, sulfhydryls, and primary, secondary or tertiary amines.

As used herein, the term "SH" refers to a sulfhydryl group. It is intended within the scope of the present invention that , whenever a "SH" or "SR" group is present, it can also be substituted by any other appropriate oxidation state such as SO**R**, SO_2**R**, or SO_3**R**.

It is intended that the term "substituted" when applied in conjunction with a radical having more than one moiety such as C_{1-6}alkyl-aryl, or C_{1-6}alkyl-**Het**, such substitution applies to both moieties i.e. both the alkyl and aryl or **Het** moieties can be substituted with the defined substituents.

As used herein, the term "COOH" refers to a carboxylic acid group. It is well known to one skilled in the art that carboxylic acid groups may be substituted by functional group equivalents. Examples of such functional group equivalents that are contemplated by this invention include, but are not limited to, esters, amides, boronic acids or tetrazole.

As used herein, the term "functional group equivalent" is intended to mean an element or a substituted derivative thereof, that is replaceable by another element that has similar electronic, hybridization or bonding properties.

As used herein, the term "metal catalyst" is intended to mean a metal such as palladium (0) or palladium (2) that is bonded to a leaving group for use in a cross-coupling reaction. Examples of such palladium catalysts include, but are not limited to, $Pd(Ph_3)_4$, Pd/C, $Pd(OAc)_2$, $PdCl_2$, and the like. Alternative metals that can catalyze cross-coupling reactions include, but are not limited to: $Ni(acac)_2$, $Ni(OAc)_2$, or $NiCl_2$.

As used herein, the term "derivative" is intended to mean "detectable label", "affinity tag" or "photoreactive group". The term "detectable label" refers to any group that may be linked to the polymerase or to a compound of the present invention such that when the compound is associated with the polymerase target, such label allows

recognition either directly or indirectly of the compound such that it can be detected, measured and quantified. Examples of such "labels" are intended to include, but are not limited to, fluorescent labels, chemiluminescent labels, colorimetric labels, enzymatic markers, radioactive isotopes and affinity tags such as biotin. Such labels are attached to the compound or to the polymerase by well known methods. The term "affinity tag" means a ligand (that is linked to the polymerase or to a compound of the present invention) whose strong affinity for a receptor can be used to extract from a solution the entity to which the ligand is attached. Examples of such ligands include biotin or a derivative thereof, a histidine polypeptide, a polyarginine, an amylose sugar moiety or a defined epitope recognizable by a specific antibody. Such affinity tags are attached to the compound or to the polymerase by well-known methods.

The term "photoreactive group" means a group that is transformed, upon activation by light, from an inert group to a reactive species, such as a free radical. Examples of such groups include, but are not limited to, benzophenones, azides, and the like.

As used herein, the term "pharmaceutically acceptable salt" includes those derived from pharmaceutically acceptable bases and is non-toxic. Examples of suitable bases include choline, ethanolamine and ethylenediamine. Na^+, K^+, and Ca^{++} salts are also contemplated to be within the scope of the invention (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19, incorporated herein by reference).

Preferred embodiments

Preferably, compounds of the present invention have the following formula I as defined above, wherein preferably:

R^1 is selected from: (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl, or **Het** each of which being optionally substituted with 1 or 2 halogen or from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, each optionally substituted with OR^{11}, SR^{11}, wherein **R^{11}** is H, $(C_{1-6}$ alkyl$)$, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

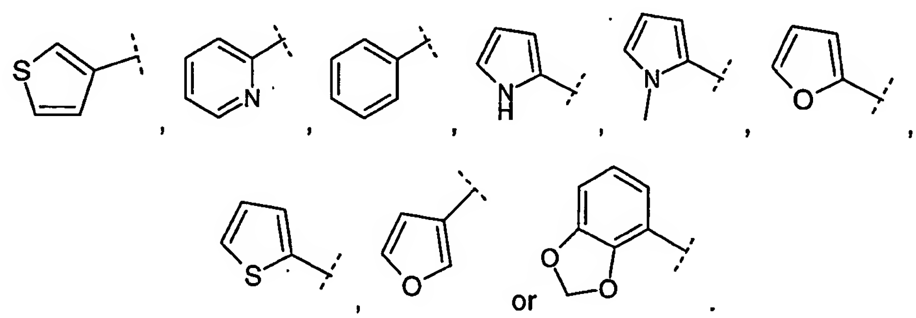
b) OR^{13} wherein **R^{13}** is H, $(C_{1-6}$ alkyl$)$, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, or **Het**; and

f) a 6- or 10-membered aryl, or **Het** said aryl or **Het** being optionally substituted with (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl.

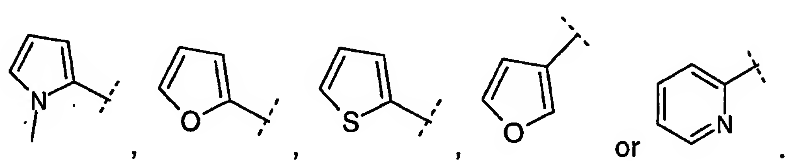
More preferably, $\mathbf{R^1}$ is selected from: 6 or 10-membered aryl, or **Het** each of which being optionally substituted with 1 or 2 halogen or with 1 or 2 (C_{1-6})alkyl or (C_{2-6})alkenyl.

Most preferably, $\mathbf{R^1}$ is phenyl or **Het** optionally substituted with (C_{1-6})alkyl.

Even most preferably, $\mathbf{R^1}$ is:

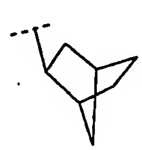


Still, even most preferably, $\mathbf{R^1}$ is:



Preferably, $\mathbf{R^2}$ is selected from (C_{3-7})cycloalkyl, (C_{6-10})bicycloalkyl, each optionally substituted with 1 or 2 substituents selected from:

a) halogen, (C_{1-6})alkyl, OH and (C_{1-6})alkoxy.

More preferably, $\mathbf{R^2}$ is selected from (C_{3-7})cycloalkyl, (C_{6-10})bicycloalkyl, each optionally mono- or di-substituted with halogen or (C_{1-6})alkyl. Most preferably, $\mathbf{R^2}$ is selected from (C_{3-7})cycloalkyl or (C_{6-10})bicycloalkyl. Even most preferably, $\mathbf{R^2}$ is cyclopentyl, cyclohexyl, or  . Still, even most preferably, $\mathbf{R^2}$ is cyclopentyl

or cyclohexyl.

Preferably, **B** is N or CR^5, wherein R^5 is H, halogen, haloalkyl or (C_{1-6})alkyl. More preferably, **B** is N, CH or C-(C_{1-6} alkyl). Most preferably, **B** is N, CH or C(Me). Even most preferably **B** is CH.

Preferably, **X** is N, CH or C(C_{1-6}) alkyl. More preferably, **X** is N, CH or C(Me). Most preferably, **X** is N or CH. Even most preferably, **X** is CH.

Preferably, **D** is CR^5, wherein R^5 is H, halogen, haloalkyl, or (C_{1-6})alkyl. More preferably, **D** is CH or C(Me). Most preferably, **D** is CH.

Preferably, Y^1 is O.
Preferably, Y^2 is O.
More preferably both Y^1 and Y^2 are O.

Preferably, **Z** is N, or NH or O. More preferably, **Z** is NH or O. Most preferably, **Z** is NH.

Preferably, R^3 and R^4 are each independently H, (C_{1-6})alkyl, first (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het** (C_{1-6})alkyl-6- or 10-membered aryl, (C_{1-6})alkyl-**Het**;
or R^3 and R^4 are covalently bonded together to form second (C_{3-7})cycloalkyl or a 5- or 6-membered heterocycle having from1 to 4 heteroatom selected from O, N, and S;

wherein said alkyl, first and second cycloalkyl, aryl, **Het** (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** or heterocycle are optionally substituted with: 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{2-4})alkenyl; and
c) OR^{31} or $COOR^{31}$, wherein R^{31} is H or (C_{1-6})alkyl;

or when **Z** is N, both R^3 or R^4 are covalently bonded thereto to form a nitrogen-containing 5-or 6-membered heterocycle.

More preferably, R^3 and R^4 are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, phenyl, **Het** (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**;

or $\mathbf{R^3}$ and $\mathbf{R^4}$ are covalently bonded together to form cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, 5- or 6-membered heterocycle having from 1 or 2 heteroatom selected from N or S;

wherein said alkyl, cycloalkyl, aryl, **Het** (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl or heterocycle are optionally substituted with from 1 or 2 substituents selected from:

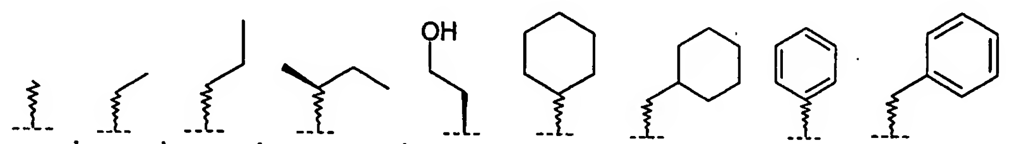
a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{2-4})alkenyl; and

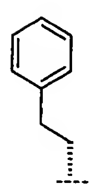
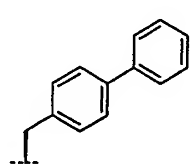
c) OH or $COO(C_{1-6})$alkyl.

Most preferably, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, phenyl, **Het** (C_{1-6})alkyl-phenyl, (C_{1-6})alkyl-**Het**; or $\mathbf{R^3}$ and $\mathbf{R^4}$ are covalently bonded together to form cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl all optionally substituted with OH, (C_{1-6} alkyl) or (C_{2-4})alkenyl; or $\mathbf{R^3}$ and $\mathbf{R^4}$ form a piperidine or a pyrrolidine both optionally substituted with (C_{1-6} alkyl) or $COO(C_{1-6})$alkyl.

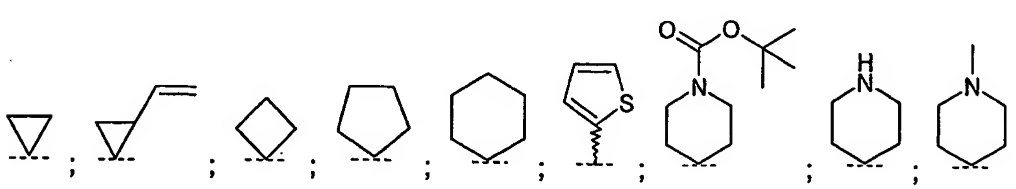
Even most preferably, $\mathbf{R^3}$ is H or (C_{1-6})alkyl and $\mathbf{R^4}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-phenyl, phenyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or (C_{1-6})alkyl-biphenyl.

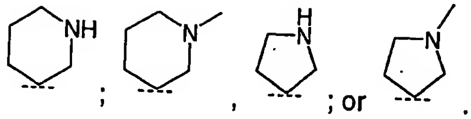
Still most preferably $\mathbf{R^3}$ and $\mathbf{R^4}$ are both H or both CH_3;
or $\mathbf{R^3}$ is H and $\mathbf{R^4}$ is selected from:



 and  ; or

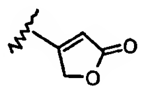
$\mathbf{R^3}$ and $\mathbf{R^4}$ are bonded together and form:





Preferably, $\mathbf{R^7}$ is H or (C_{1-6} alkyl). More preferably, $\mathbf{R^7}$ is H or Me. Most preferably, $\mathbf{R^7}$ is H.

Preferably, **A** is 6- or 10-membered aryl, **Het** or (C_{1-6})alkyl-CONH-aryl, said aryl and **Het** being optionally substituted with:



, -halogen, or

- 1 to 2 substituents selected from:

  a) (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which are optionally substituted with:

    - (C_{1-6})alkyl or (C_{3-7})cycloalkyl, both optionally substituted with a 6 or 10-membered aryl or **Het**;
    - $\mathbf{OR^{101}}$ or $\mathbf{COOR^{101}}$ wherein each $\mathbf{R^{101}}$ is independently H or (C_{1-6})alkyl;

  b) $\mathbf{OR^{104}}$ wherein $\mathbf{R^{104}}$ is H or (C_{1-6}alkyl) optionally substituted with: COOH or COO(C_{1-6})alkyl;

  d) $\mathbf{SR^{108}}$, wherein $\mathbf{R^{108}}$ is H or (C_{1-6})alkyl optionally substituted with COOH or COO(C_{1-6})alkyl;

  e) $\mathbf{NR^{111}R^{112}}$ wherein $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are both H; or $\mathbf{R^{111}}$ is H and $\mathbf{R^{112}}$ is **Het** optionally substituted with (C_{1-6})alkyl or $\mathbf{COOR^{115}}$ wherein $\mathbf{R^{115}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

  j) tetrazole, COOH or COO(C_{1-6})alkyl;

  k) $\mathbf{CONR^{129}R^{130}}$ wherein $\mathbf{R^{129}}$ and $\mathbf{R^{130}}$ are each independently H or (C_{1-6})alkyl optionally substituted with COOH or COO(C_{1-6})alkyl; and

  l) 6- or 10-membered aryl or **Het** said aryl or **Het** being optionally substituted with from 1 to 4 substituents selected from:

    i) (C_{1-6})alkyl or haloalkyl;

    ii) $\mathbf{OR^{104}}$ wherein $\mathbf{R^{104}}$ is H, or (C_{1-6})alkyl) optionally substituted with COOH or COO(C_{1-6})alkyl; and

iii) $COOR^{128}$, $NR^{111}R^{112}$ or $CON(R^{129}R^{130})_2$, wherein R^{128}, R^{111}, R^{112}, R^{129} and R^{130} are independently H or (C_{1-6})alkyl.

More preferably **A** is a 6- or 10-membered aryl, or **Het** said aryl or **Het** being optionally substituted with:

-halogen, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, said alkyl and alkenyl being optionally substituted with:

- OH, (C_{1-6})alkoxy, or COOH;

b) OH or $O(C_{1-6})$alkyl)COOH;

d) SH or $S(C_{1-6})$alkylCOOH;

j) tetrazole or COOH; and

l) furan or thiazole mono or di- substituted with:

i) (C_{1-6})alkyl; or

iii) COOH or $CONH_2$.

Most preferably, **A** is phenyl, indole, benzofuran, benzothiophene, coumarin or quinolone, all of which being optionally substituted with:

-iodine, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, said alkyl and alkenyl being optionally substituted with:

- OH, (C_{1-6})alkoxy, or COOH;

b) OH or $O(C_{1-6})$alkyl)COOH;

d) SH or $S(C_{1-6})$alkylCOOH;

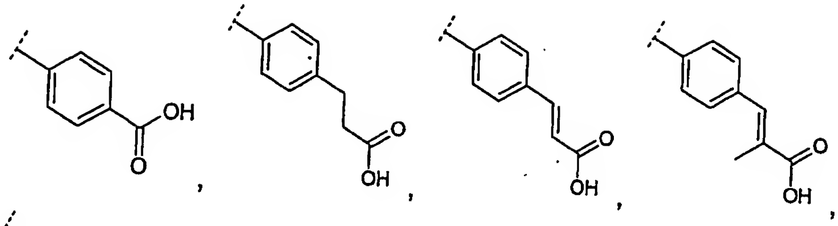
j) COOH; and

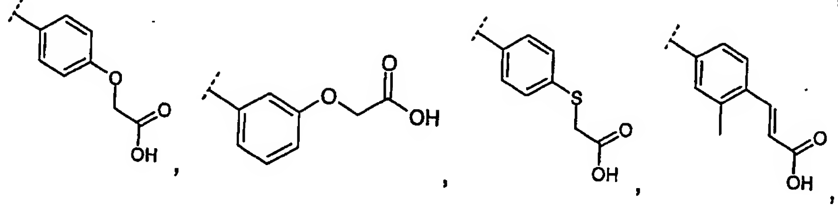
l) furan or thiazole mono or di- substituted with:

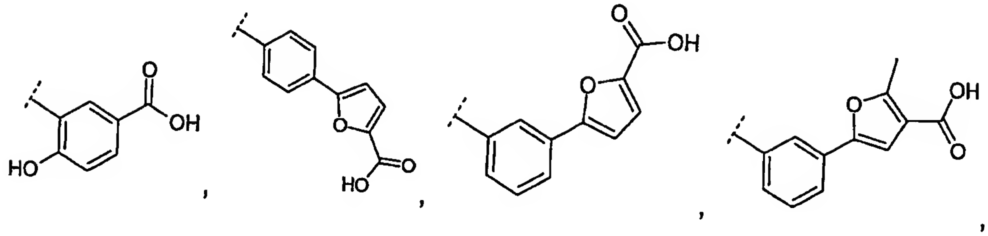
i) (C_{1-6})alkyl; or

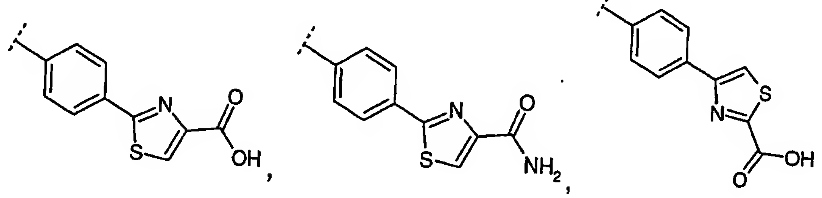
iii) COOH or $CONH_2$.

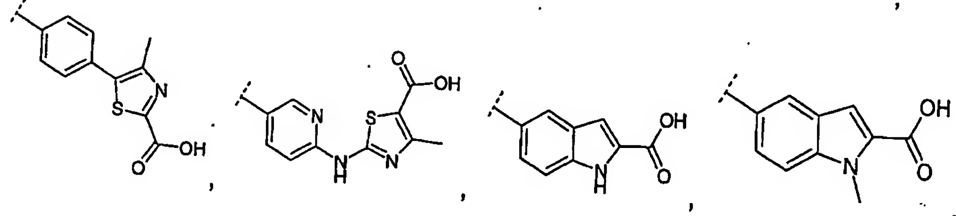
Even most preferably **A** is

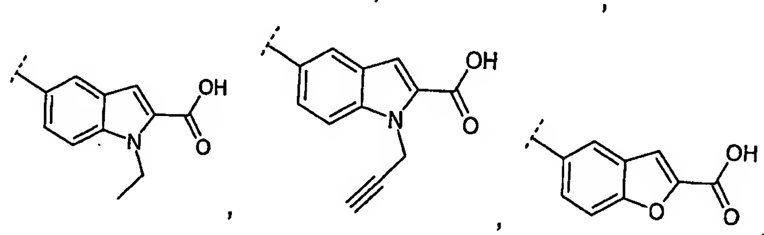


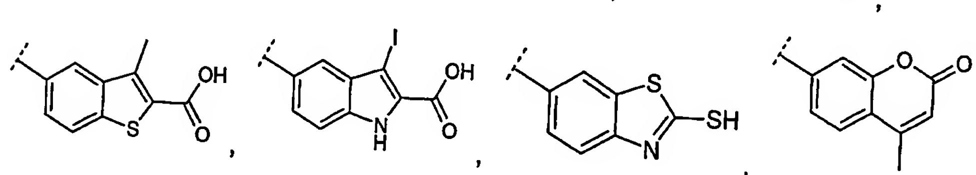




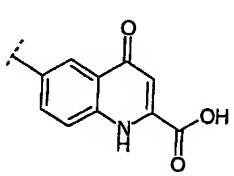






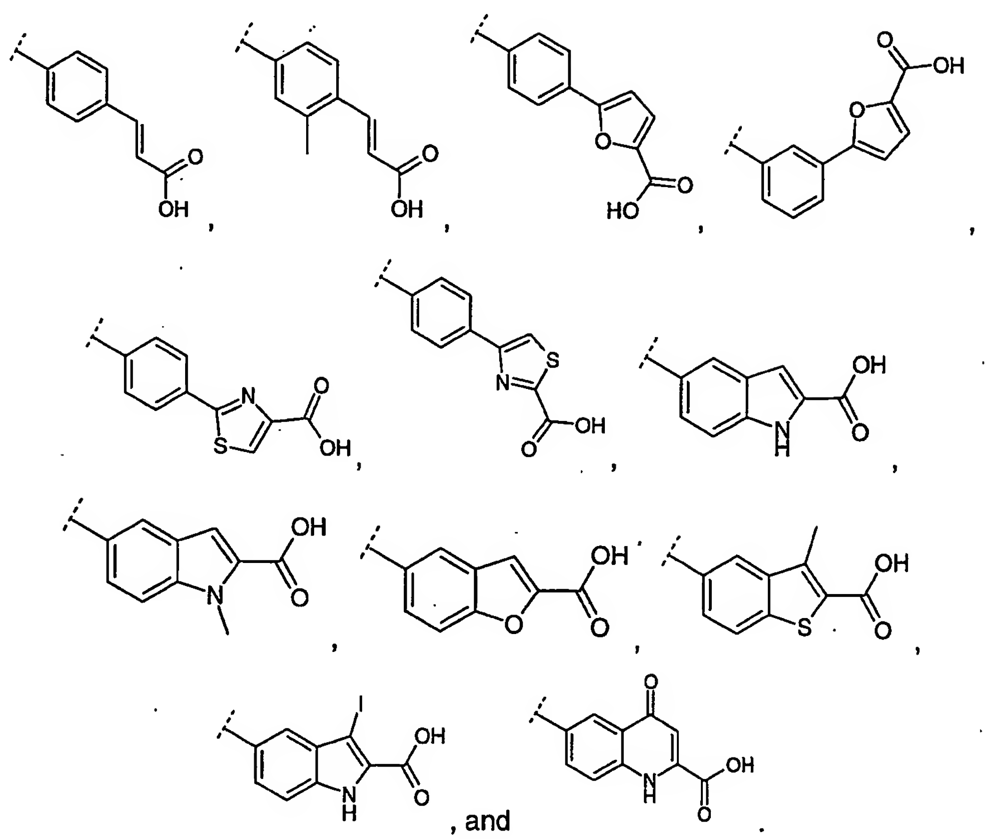


and

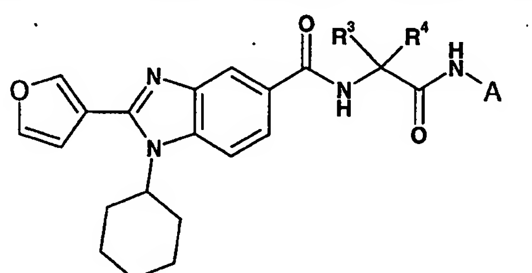


.

Sill, even most preferably **A** is selected from:



Preferably, compounds of the invention have the following formula:



II

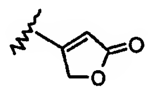
wherein $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently H, (C_{1-6})alkyl, first (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het** (C_{1-6})alkyl-6- or 10-membered aryl, (C_{1-6})alkyl-**Het**;
or $\mathbf{R^3}$ and $\mathbf{R^4}$ are covalently bonded together to form second (C_{3-7})cycloalkyl or a 5- or 6-membered heterocycle having from1 to 4 heteroatom selected from O, N, and S;

wherein said alkyl, first and second cycloalkyl, aryl, **Het** (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** or heterocycle are optionally substituted with from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{2-4})alkenyl; and

c) OR^{31} or $COOR^{31}$, wherein each R^{31} is independently H or (C_{1-6})alkyl; and

A is a 6- or 10-membered aryl, **Het**, or (C_{1-6}) alkyl-CONH-aryl, said aryl or **Het** being optionally substituted with:



, halogen, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which are optionally substituted with:

- (C_{1-6})alkyl, (C_{3-7})cycloalkyl, both optionally substituted with a 6 or 10-membered aryl, or **Het**;

b) OR^{101}, or $COOR^{101}$ wherein R^{101} is H or (C_{1-6})alkyl;

b) OR^{104} wherein R^{104} is H or $(C_{1-6}$alkyl) optionally substituted with: COOH or $COO(C_{1-6})$alkyl;

c) SR^{108} wherein R^{108} is H or (C_{1-6})alkyl optionally substituted with COOH or $COO(C_{1-6})$alkyl;

d) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are H; or R^{111} is H and R^{112} is **Het** optionally substituted with (C_{1-6})alkyl or $COOR^{115}$ wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

e) COOH or $COO(C_{1-6})$alkyl; and

f) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H or (C_{1-6})alkyl optionally substituted with COOH or $COO(C_{1-6})$alkyl; and

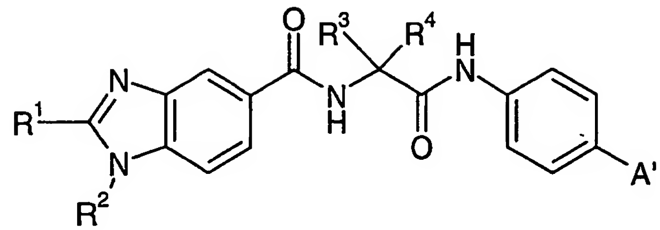
g) 6- or 10-membered aryl or **Het** said aryl or **Het** being optionally substituted with from 1 to 4 substituents selected from:

i) (C_{1-6})alkyl or haloalkyl;

ii) OR^{104} wherein R^{104} is H or (C_{1-6})alkyl) optionally substituted with COOH or $COO(C_{1-6})$alkyl; and

iii) $COOR^{128}$, $NR^{111}R^{112}$ or $CON(R^{129}R^{130})_2$, wherein R^{128}, R^{111}, R^{112}, R^{129} and R^{130} are independently H or (C_{1-6})alkyl.

Preferably, compounds of the invention have the following formula:



III

wherein

R^1 is selected from: (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het** each of which being optionally substituted with 1 or 2 halogen or from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, each optionally substituted with **OR**^{11} or **SR**^{11} wherein **R**^{11} is H, $(C_{1-6}$ alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

b) **OR**^{13} wherein **R**^{13} is H, $(C_{1-6}$ alkyl), (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, or **Het**; and

f) a 6- or 10-membered aryl, or **Het** said aryl or **Het** being optionally substituted with (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

R^2 is selected from (C_{3-7})cycloalkyl, (C_{6-10})bicycloalkyl, each optionally substituted with 1 or 2 substituents selected from: halogen, (C_{1-6})alkyl, OH, and (C_{1-6})alkoxy;

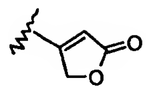
R^3 and **R**^{4} are each independently H, (C_{1-6})alkyl, first (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het** (C_{1-6})alkyl-6- or 10-membered aryl, (C_{1-6})alkyl-**Het**;
or **R**^{3} and **R**^{4} are covalently bonded together to form second (C_{3-7})cycloalkyl, 5- or 6-membered heterocycle having from1 to 4 heteroatom selected from O, N, and S;

wherein said alkyl, first and second cycloalkyl, aryl, **Het** (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** or heterocycle are optionally substituted with from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{2-4})alkenyl; and

c) **OR**^{31} or **COOR**^{31}, wherein **R**^{31} is H or (C_{1-6})alkyl; and

A' is a 6- or 10-membered aryl, **Het**, or (C_{1-6}) alkyl-CONH-aryl, said aryl or **Het** being optionally substituted with:

, halogen, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which are optionally substituted with:

second (C_{1-6})alkyl or second (C_{3-7})cycloalkyl, said second alkyl or second cycloalkyl being optionally substituted with a 6 or 10-membered aryl or **Het**;

b) OR^{101} or $COOR^{101}$ wherein each R^{101} is independently H or (C_{1-6})alkyl;

b) OR^{104} wherein R^{104} is H or $(C_{1-6}$alkyl) optionally substituted with: COOH or COO(C_{1-6})alkyl;

c) SR^{108}, wherein R^{108} is H or (C_{1-6})alkyl optionally substituted with COOH or COO(C_{1-6})alkyl;

d) $NR^{111}R^{112}$ wherein R^{111} and R^{112} are both H; or R^{111} is H and R^{112} is **Het** optionally substituted with (C_{1-6})alkyl or $COOR^{115}$ wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; COOH or COO(C_{1-6})alkyl;

e) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are each independently H or (C_{1-6})alkyl optionally substituted with COOH or COO(C_{1-6})alkyl; and

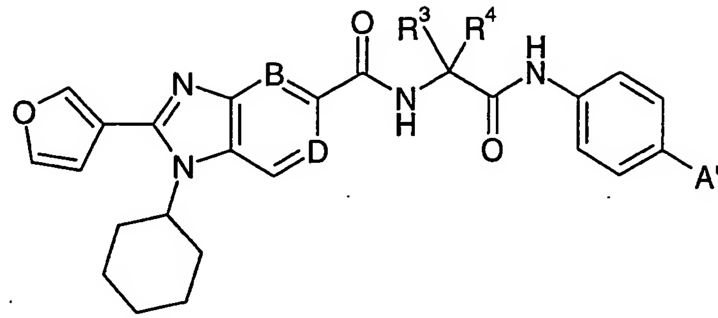
f) 6- or 10-membered aryl or **Het,** said aryl or **Het** being optionally substituted with from 1 to 4 substituents selected from:

i) (C_{1-6})alkyl or haloalkyl;

ii) OR^{104} wherein R^{104} is H, or (C_{1-6})alkyl) optionally substituted with COOH or COO(C_{1-6})alkyl; and

iii) $COOR^{128}$, $NR^{111}R^{112}$ or $CON(R^{129}R^{130})_2$, wherein R^{128}, R^{111}, R^{112}, R^{129} and R^{130} are independently H or (C_{1-6})alkyl.

Preferably, compounds of the invention have the following formula:



IV

wherein

D is CH or C(C_{1-6})alkyl;

B is N, CH, or C(C_{1-6})alkyl;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently H, (C_{1-6})alkyl, first (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het** (C_{1-6})alkyl-6- or 10-membered aryl, (C_{1-6})alkyl-**Het**;

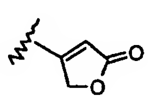
or $\mathbf{R^3}$ and $\mathbf{R^4}$ are covalently bonded together to form second (C_{3-7})cycloalkyl, 5- or 6-membered heterocycle having from1 to 4 heteroatom selected from O, N, and S;

wherein said alkyl, first and second cycloalkyl, aryl, **Het** (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** or heterocycle are optionally substituted with from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{2-4})alkenyl; and

c) $\mathbf{OR^{31}}$ or $\mathbf{COOR^{31}}$, wherein $\mathbf{R^{31}}$ is H or (C_{1-6})alkyl; and

A' is a 6- or 10-membered aryl, **Het** or (C_{1-6}) alkyl-CONH-aryl, said aryl or **Het** being optionally substituted with:

, -halogen, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which are optionally substituted with:

- second (C_{1-6})alkyl or second (C_{3-7})cycloalkyl, said second alkyl or second cycloalkyl being optionally substituted with a 6 or 10-membered aryl or **Het**;

- $\mathbf{OR^{101}}$ or $\mathbf{COOR^{101}}$ wherein each $\mathbf{R^{101}}$ is independently H or (C_{1-6})alkyl;

b) $\mathbf{OR^{104}}$ wherein $\mathbf{R^{104}}$ is H or (C_{1-6}alkyl) optionally substituted with: COOH or COO(C_{1-6})alkyl;

d) $\mathbf{SR^{108}}$, wherein $\mathbf{R^{108}}$ is H or (C_{1-6})alkyl optionally substituted with

COOH or COO(C_{1-6})alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} and R^{112} are both H; or R^{111} is H and R^{112} is **Het** optionally substituted with (C_{1-6})alkyl or $COOR^{115}$ wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

f) COOH or COO(C_{1-6})alkyl;

g) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are each independently H or (C_{1-6})alkyl optionally substituted with COOH or COO(C_{1-6})alkyl; and

h) 6- or 10-membered aryl or **Het** said aryl or **Het** being optionally substituted with from 1 to 4 substituents selected from:

i) (C_{1-6})alkyl or haloalkyl;

ii) OR^{104} wherein R^{104} is H, or (C_{1-6})alkyl) optionally substituted with COOH or COO(C_{1-6})alkyl; and

iii) $COOR^{128}$, $NR^{111}R^{112}$ or $CON(R^{129}R^{130})_2$, wherein R^{128}, R^{111}, R^{112}, R^{129} and R^{130} are independently H or (C_{1-6})alkyl.

Specific embodiments

Included within the scope of this invention are all compounds of formula I as presented in Tables 1 to 3.

Polymerase activity

The ability of the compounds of formula I to inhibit RNA synthesis by the RNA dependent RNA polymerase of HCV can be demonstrated by any assay capable of measuring RNA dependent RNA polymerase activity. A suitable assay is described in the examples.

Specificity for RNA dependent RNA polymerase activity

To demonstrate that the compounds of the invention act by specific inhibition of HCV polymerase, the compounds may be tested for inhibitory activity in a DNA dependent RNA polymerase assay.

When a compound of formula I or one of its therapeutically acceptable salts, is employed as an antiviral agent, it is administered orally, topically or systemically to mammals, e.g. humans, rabbits or mice, in a vehicle comprising one or more

pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice.

For oral administration, the compound of formula I or a therapeutically acceptable salt thereof can be formulated in unit dosage forms such as capsules or tablets each containing a predetermined amount of the active ingredient, ranging from about 25 to 500 mg, in a pharmaceutically acceptable carrier.

For topical administration, the compound of formula I can be formulated in pharmaceutically accepted vehicles containing 0.1 to 5 percent, preferably 0.5 to 5 percent, of the active agent. Such formulations can be in the form of a solution, cream or lotion.

For parenteral administration, the compound of formula I is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. For administration by injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic.

Suitable vehicles or carriers for the above noted formulations are described in pharmaceutical texts, e.g. in "Remington's The Science and Practice of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms And Drugs Delivery Systems", 6th ed., H.C. Ansel et al., Eds., Williams & Wilkins, Baltimore, Maryland, 1995.

The dosage of the compound will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small increments until the optimum effect under the circumstance is reached. In general, the compound of formula I is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

For oral administration, the compound of formula I or a therapeutically acceptable salt is administered in the range of 10 to 200 mg per kilogram of body weight per day, with a preferred range of 25 to 150 mg per kilogram.

For systemic administration, the compound of formula I is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the aforementioned variations will occur. A dosage level that is in the range of from about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

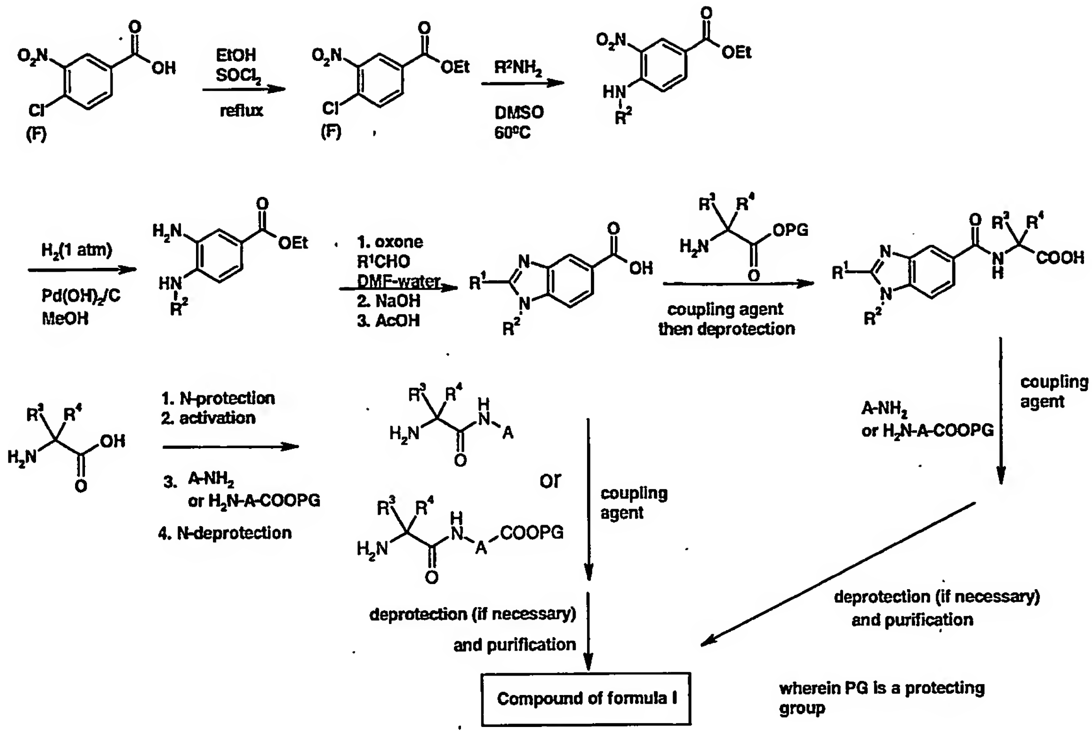
When the compositions of this invention comprise a combination of a compound of formula I and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

When these compounds or their pharmaceutically acceptable salts are formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered *in vivo* to mammals, such as man, to inhibit HCV polymerase or to treat or prevent HCV virus infection. Such treatment may also be achieved using the compounds of this invention in combination with agents which include, but are not limited to: immunomodulatory agents, such as α-, β-, δ-, or γ-interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of HCV NS5B polymerase; inhibitors of other targets in the HCV life cycle, which include but are not limited to, helicase, NS2/3 protease, NS3 protease, or internal ribosome entry site (IRES); or combinations thereof. The additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Methodology and Synthesis

Benzimidazole derivatives or analogs according to the present invention can be prepared from known starting materials by following Scheme 1, shown below wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^7}$, and **A** are as described herein.

Scheme 1



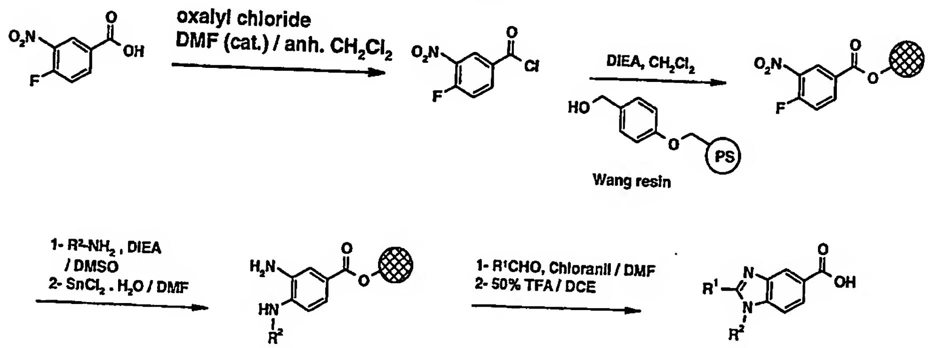
In carrying out the route illustrated in Scheme 1, a suitably protected form of 4-chloro-3-nitrobenzoic acid or 4-fluoro-3-nitrobenzoic acid is reacted with a primary amine R^2NH_2. Amines are of commercial sources or can be prepared by literature methods. This reaction is carried out in a suitable solvent such as DMSO, DMF or the like, at temperatures ranging from 20 °C to 170 °C, or alternatively without solvent by heating the two components together. The nitro group of these derivatives is subsequently reduced to the corresponding aniline, using a reducing agent such as hydrogen gas or a formate salt in the presence of a catalyst (e.g. Pd metal and the like), metals in the presence of mineral acids (e.g. Fe or Zn with aqueous HCl), or metal salts ($SnCl_2$). The diamino derivatives that are obtained are condensed with commercially available aldehydes R^1CHO in the presence of an oxidizing agent (e.g. air, oxygen, iodine, oxone®, quinones, peroxides etc.) to give benzimidazole 5-carboxylates.

Alternatively, other methods for benzimidazole ring construction can be employed, such as condensation of the diamino derivatives with carboxylic acids, nitriles or amides, in the presence or absence of a catalyst. Such methods are well known in the literature to those skilled in the art. Saponification of the ester protecting group of such derivatives using alkali metal hydroxides, followed by neutralization with

weak acids (e.g. AcOH) generates free 5-carboxybenzimidazoles.

Alternatively, 5-carboxybenzimidazole derivatives such as those described above can be prepared on a solid support as described in Scheme 2:

Scheme 2



In carrying out the synthetic route illustrated in Scheme 2, 4-fluoro-3-nitrobenzoic acid is converted to the acid chloride derivative using standard procedures (e.g. thionyl chloride, oxalyl chloride, phosgene and the like in the presence of a catalytic amount of DMF) in an inert solvent such as DCM. Wang resin is esterified with this acid chloride by condensation in the presence of an organic tertiary amine such as Et_3N, *N*-methylmorpholine, DIEA and the like. Other types of resins are well known to those skilled in the art, for example Rink resin, which may be functionalized without deviating from the scope of the invention. The functionalized resin thus obtained is then elaborated to resin-bound benzimidazole carboxylate derivatives as described above for the solution-phase chemistry. Cleavage of the benzimidazole from the resin is carried out with strong acids (e.g. trifluoroacetic acid) to give benzimidazole 5-carboxylic acids.

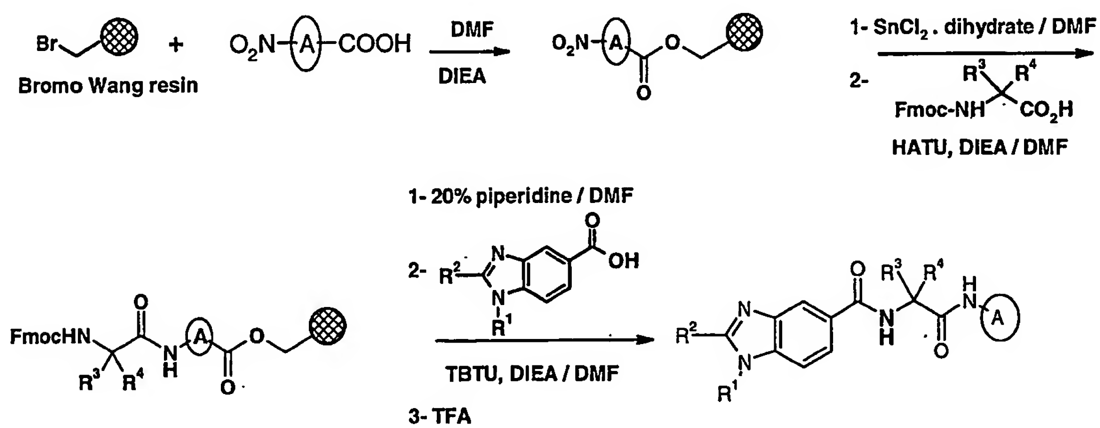
Derivatives of formula I may be obtained by condensation of 5-carboxybenzimidazole derivatives such as those described above with suitably protected forms of an amino acid derivative $H_2NCR^3R^4COOPG$ (where PG serves as a carboxylic acid protecting group, e.g. Me, Et, tBu etc.) through formation of an amide bond. Condensation of the carboxylic acid with $H_2NCR^3R^4COOPG$ can be accomplished using standard peptide bond forming reagents such as TBTU, HATU, BOP, BroP, EDAC, DCC, isobutyl chloroformate, PCl_5 and the like, or by activation of the carboxyl group by conversion to the corresponding acid chloride prior to condensation with the amino acid derivative. This coupling reaction is then followed by deprotection of the ester (COOPG) to a free carboxylic acid group which is then condensed with amine

derivatives of formula H_2N-A to provide compounds of formula I after removal of any remaining protecting groups.

Alternatively, *N*-protected amino acid derivatives of formula $P'HNCR^3R^4COOH$ (where P' is a nitrogen protecting group such as Boc, Cbz, Fmoc and the like) are coupled to amine derivatives of formula H_2N-A using standard amide bond forming reagents as described above. Following removal of the nitrogen protecting group from the amide derivative thus obtained, the free amine can be coupled to 5-carboxybenzimidazole derivatives through formation of a second amide linkage as described above. Following removal of any remaining protecting groups, compounds of formula 1 are obtained.

Alternatively, compounds of formula 1 according to the present invention can be prepared on a solid support as described in Scheme 3.

Scheme 3



In carrying out the synthetic route illustrated in Scheme 3, derivatives of formula O_2N-A (where A contains a free carboxyl group) are anchored on a solid support. Such support includes bromo Wang resin, and attachment is carried out using a suitable base such as DIEA, CsF or others well known to those trained in the field of peptide synthesis on solid supports. Following reduction of the nitro group to a free amine using reducing agents such as hydrogen gas or formate salts in the presence of a catalyst (e.g. Pd metal and the like), metals in the presence of mineral acids (e.g. Fe or Zn with aqueous HCl), or metal salts ($SnCl_2$), the free amine is coupled to a suitably *N*-protected form of an amino acid of formula $P'HNCR^3R^4COOH$ (P' is an

amino acid *N*-protecting group such as Fmoc). Suitable coupling reagents include HATU, TBTU, BOP, EDAC, DCC, isobutyl chloroformate and others, in presence of an organic tertiary base such as DIEA, Et_3N, NMM and the like. Acid chlorides can also be used in the case of hindered amino acid derivatives. Following removal of the nitrogen-protecting group, the resulting amine is coupled to 5-carboxybenzimidazole derivatives with standard amide bond forming reagents as described previously. Compounds of formula 1 where **A** contains a free carboxylic acid group are obtained after cleavage from the resin under acidic conditions (TFA, MsOH, TfOH and the like).

EXAMPLES

The present invention is illustrated in further detail by the following non-limiting examples. All reactions were performed in a nitrogen or argon atmosphere. Temperatures are given in degrees Celsius. Solution percentages or ratios express a volume to volume relationship, unless stated otherwise. Flash chromatography was carried out on silica gel. Mass spectral analyses were recorded using electrospray mass spectrometry. Abbreviations or symbols used herein include:
DIEA: diisopropylethylamine;
DMAP: 4-(dimethylamino)pyridine;
DMSO: dimethylsulfoxide;
DMF: *N,N*-dimethylformamide;
Et: ethyl;
EtOAc: ethyl acetate;
Et_2O: diethyl ether;
HPLC: high performance liquid chromatography;
^{i}Pr: isopropyl
Me: methyl;
MeOH: methanol;
MeCN: acetonitrile;
Ph: phenyl;
TBE: tris-borate-EDTA;
TBTU: 2-(*1H*-benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate;
TFA: trifluoroacetic acid;
THF: tetrahydrofuran;

MS (ES): electrospray mass spectrometry;

PFU: plaque forming units;

DEPC: diethyl pyrocarbonate;

DTT: dithiothreitol

EDTA: ethylenediaminetetraacetate

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

BOP: benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate

BroP: bromotris(dimethylamino)-phosphonium hexafluorophosphate

EDAC: see EDC

DCC: 1,3-Dicyclohexyl carbodiimide

DCE: 1,2-dichloroethane

HOBt: 1-Hydroxybenzotriazole

ES^+: electrospray (positive ionization)

ES^-: electrospray (negative ionization)

DCM: dichloromethane

TBME: *tert*-butylmethyl ether

TLC: thin layer chromatography

CSA: camphorsulfonic acid

AcOH: acetic acid

EtOH: ethanol

DBU: 1,8-diazabicyclo[5.4.0]under-7-ene

BOC: *tert*-butyloxycarbonyl

Cbz: carbobenzyloxy carbonyl

^{i}PrOH: isopropanol

NMP: *N*-methylpyrrolidone

NMM: *N*-methylmorpholine

EDC: 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride

RNAsin: A ribonuclease inhibitor marketed by Promega Corporation

Tris: 2-amino-2-hydroxymethyl-1,3-propanediol

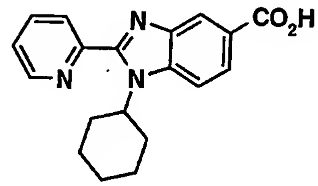
UMP: uridine 5'-monophosphate

UTP: uridine 5'-triphosphate

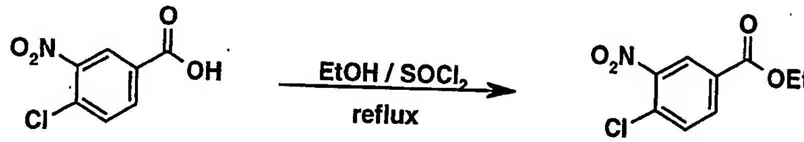
Examples 1-21 illustrate methods of synthesis of representative compounds of this invention.

Example 1:

1-Cyclohexyl-2-pyridin-2-yl-1H-benzoimidazole-5-carboxylic acid:

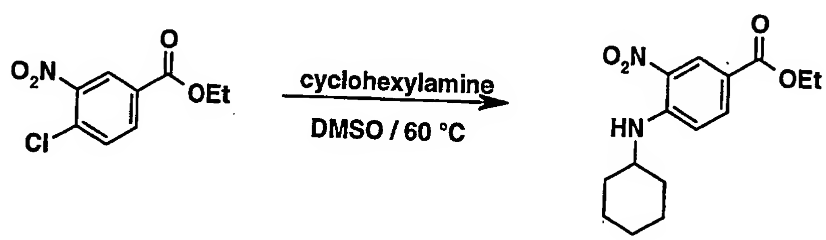


4-Chloro-3-nitrobenzoic acid, ethyl ester:



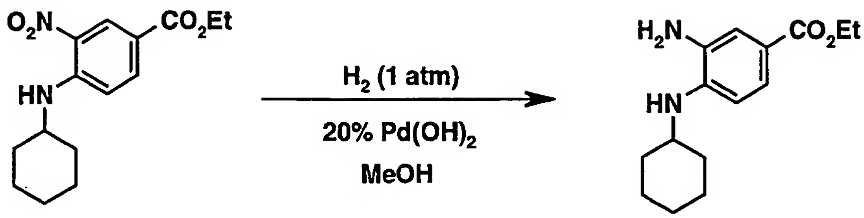
4-Chloro-3-nitrobenzoic acid (100.0 g, 0.496 mole) was suspended in EtOH (250 mL) and thionyl chloride (54 mL, 0.74 mole) was added drop-wise over 15 min. The mixture was then reflux for 2 h. After cooling to ambient temperature, volatiles were removed under reduced pressure and the residue was co-evaporated twice with EtOH (2 X 250 mL). The residue was crystallized from hot EtOH to give the desired ethyl ester as light yellow needles (109.8 g, 96% yield).

4-Cyclohexylamino-3-nitrobenzoic acid ethyl ester:



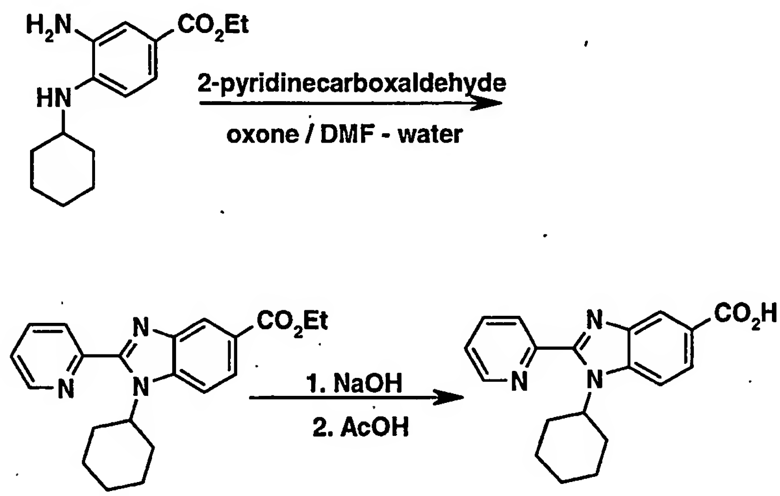
Ethyl 4-chloro-3-nitrobenzoate (20.00 g, 87 mmol) was dissolved in DMSO (50 mL) and cyclohexylamine (2.1 equiv. 21 mL, 183 mmol) was added and the mixture stirred at 60 °C for 5 h. After cooling to ambient temperature, the reaction mixture was added drop-wise with vigorous stirring to water (500 mL). After stirring for an additional 15 min, the precipitated solid was collected by filtration, washed with water and dried. The title compound (25.67 g, 100% yield) was obtained as a bright yellow solid.

3-Amino-4-cyclohexylamino benzoic acid ethyl ester:



The nitro derivative from above (24.28 g, 83 mmol) was hydrogenated (1 atm H_2) over 20% $Pd(OH)_2$ on carbon (200 mg) in MeOH (150 mL) for 3 days. The catalyst was removed by filtration and volatiles removed under reduced pressure to give the title diamine (21.72 g, 100 % yield) as a dark purple solid.

***1-Cyclohexyl-2-pyridin-2-yl-1H-benzoimidazole-5-carboxylic acid*:**

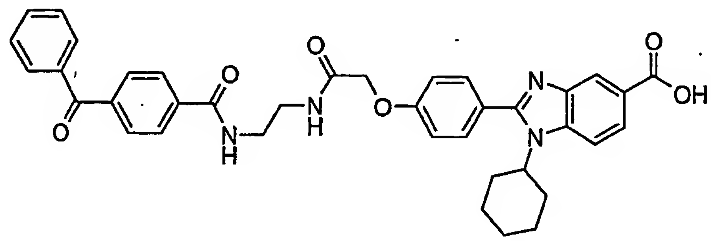


The diamine from above (3.20 g, 12.2 mmol) was dissolved in DMF (15 mL) and water (0.5 mL). 2-Pyridine carboxaldehyde (1.45 mL, 15 mmol) was added followed by oxone® (0.65 equivalent, 8 mmol, 4.92 g). The mixture was stirred 1 h at room temperature. Water (60 mL) was added, and the pH of the reaction mixture was brought up to 9 by addition of 1 N NaOH. The brown precipitate that formed was collected by filtration, washed with water and dried. The crude benzimidazole ethyl ester was obtained in 80% yield (3.43 g).

The ester from above (2.36 g, 7.53 mmol) was dissolved in MeOH (15 mL) and 2 N NaOH (20 mmol, 10 mL) was added. The mixture was stirred at 60 °C for 2 h and then cooled to room temperature. MeOH was removed under reduced pressure and the residue acidified to pH 4 with glacial AcOH. The precipitated carboxylic acid was collected by filtration, washed with water and dried to give the free acid as a beige solid (2.20 g, 91% yield).

Example 2

1-Cyclohexyl-2-(4-{[2-({1-[4-(1-phenyl-methanoyl)-phenyl]-methanoyl}-amino)-ethylcarbamoyl]-methoxy}-phenyl)1H-benzimidazole-5-carboxylic acid

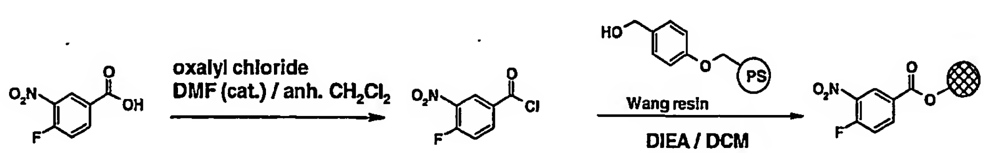


4-Formylphenoxyacetic acid (1.50 g, 8.32 mmol) in CH_2Cl_2 (25 ml) was stirred at RT with TBTU (2.75 g, 8.56 mmol) and DIPEA (2.8 g, 3.8 ml, 20 mmol) before addition of tert-butyl N-(2-aminoethyl)carbamate (1.38 g, 8.60 mmol). After stirring for 2.5 h, the solution was concentrated and the residue dissolved in EtOAc. The solution was successively washed with 5% water, 5% $KHSO_4$, brine and organic phase dried ($MgSO_4$). The dried solution was concentrated under reduced pressure to give a beige solid, which after purification using flash chromatography on silica gel with EtOAc gave the aldehyde as a white solid (2.0 g, 75%).

The aldehyde derivative from above (3.30g, 10.23 mmol) and the diamine derivative of example 1 (0.052 g, 0.1 mmol) were condensed with Oxone using a procedure similar to that described in Example 1 above. After removal of the Boc group under standard acidic conditions, benzoylbenzoic acid (900mg, 3.98 mmol) and an amide bond coupling agent, such as TBTU, were used to form the title compound after saponification, under standard conditions, of the carboxyl protecting group.

Example 3:

Solid phase synthesis of 5-carboxybenzimidazole derivatives from aldehydes:

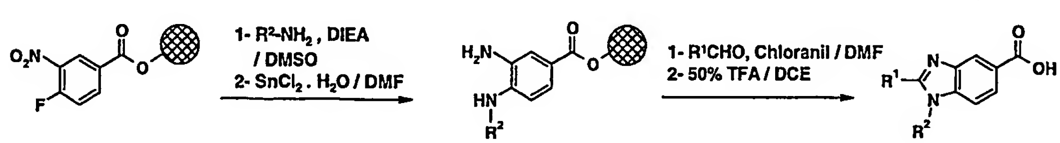


To a solution of the 4-fluoro-3-nitrobenzoic acid (0.12 mol, 22.2 g) in 100 mL of anhydrous DCM was added 10 drops of anhydrous DMF. To this solution was

added drop wise over 60 min, oxalyl chloride (0.144 mol, 12.6 mL). During the addition, the solid slowly dissolved to give rise to a yellow solution. The mixture was stirred for an additional 4 h and the solvent was stripped down to give a yellow oil. This oil was distilled under vacuum (110 °C, 1.5 mm Hg) to give 4-fluoro-3-nitrobenzoyl chloride as a light yellow liquid (22.0 g, 90% yield).

On a solid phase synthesizer (Advanced Chemtech ACT 90), Wang resin (Nova Biochem, loading: 1.2 mmol/g, 20 mmol, 16.7 g) was washed twice with DCM (100 mL), twice with *i*-PrOH (100 mL) and was dried overnight under high vacuum over P_2O_5. The following day, the resin was washed with anhydrous DCM (2 x 100 mL) and was suspended in anhydrous DCM (100 mL). To the suspension was added DIEA (30 mmol, 5.2 mL) followed by a solution of 4-fluoro-3-nitrobenzoyl chloride (22 mmol, 4.48 g) dissolved in 10 ml of anhydrous DCM. The slurry was shaken for 3 h, the solution was drained and the resin was washed twice with 100 mL-portions of anhydrous DCM. The resin was then suspended in anhydrous DCM (100 mL) and was treated with DIEA (30 mmol, 5.2 mL) followed by acetic anhydride (24 mmol, 2.3 mL). After shaking for 2 h, the solution was drained and the resin was washed successively with DCM (2 x 100 mL), *i*-PrOH (2 x 100 mL), DCM (2 x 100 mL) and finally with *i*-PrOH (3 x 100 mL). The resin was dried overnight under high vacuum. To calculate the level of incorporation, the resin (45.9 mg) was treated with a 1:1 mixture of TFA/1,2-DCE (1.5 mL) for 1 h. The resin was filtered and was washed twice with 1,2-DCE (1.5 mL). The filtrates were combined and concentrated under vacuum. The residue was lyophilized from MeCN/H_2O to give 4-fluoro-3-nitro benzoic acid as a yellow solid (6.3 mg, 0.033 mmol). Based on recovered compound, the loading was calculated to be 0.74 mmol/g.

The following steps were performed on a solid-phase synthesizer (ACT 496 from Advanced Chemtech), using the 96-well reaction block:



Amine addition:

Each well was filled with the benzoic acid resin from above (0.03 mmol, 40 mg) and was washed with DMF (3 x 1.2 mL) and DMSO (2 x 1.2 mL). To each well was

added DMSO (530 µL), a 1 M solution in DMSO of the amine R^2-NH_2 (600 µL, 0.6 mmol) and DIEA (0.4 mmol, 70 µL). The resins were shaken for 15 h at room temperature and the solvent was drained. The resins were washed successfully with 1.2-mL portions of DMF (3 x), MeOH (3 x), and DMF (4 x).

Reduction of the nitro group:

The resins were then suspended in DMF (600 µL) and were shaken with a 1 M DMF solution of $SnCl_2.2\ H_2O$ (600 µL, 0.6 mmol) for 25 h. The solvent was drained, the resins were washed successively with 1.2-mL portions of 1:1 DMF-H_2O (4 x), DMF (4 x), MeOH (4 x) and NMP (4 x).

Formation of the benzimidazole ring:

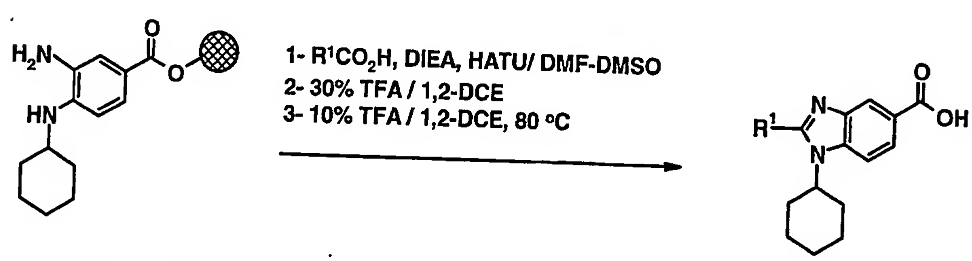
Each resin was suspended in DMF (200 µL) and a 1 M solution of the aldehyde in DMF was added (0.20 mmol, 200 µL), followed by a 0.25 M solution of chloranil in NMP (0.20 mmol, 800 µL). The resins were shaken for 18 h, the liquid was drained and the resins were washed successively with 1.2-mL portions of NMP (3 x), 1 M DIEA/NMP (2 x), NMP (3 x), MeOH (3 x) and DCM (4 x). The reaction block was placed in a vacuum chamber for 30 min in order to dry the resin.

Cleavage from the resin:

In each well was added 1.0 mL of a 1:1 solution of TFA/1,2-DCE and the resins were shaken for 1 h. The wells were drained and the resins washed once with 1.0 mL of the cleavage solution. Volatiles were evaporated in a vacuum centrifuge to give the crude benzimidazole 5-carboxylic.

EXAMPLE 4:

Solid phase synthesis of 5-carboxybenzimidazole derivatives from carboxylic acids:



The following steps were performed on a solid-phase synthesizer (ACT 496 from Advanced Chemtech), using the 96-well reaction block.

The starting diamine resin was prepared as described in example 3.

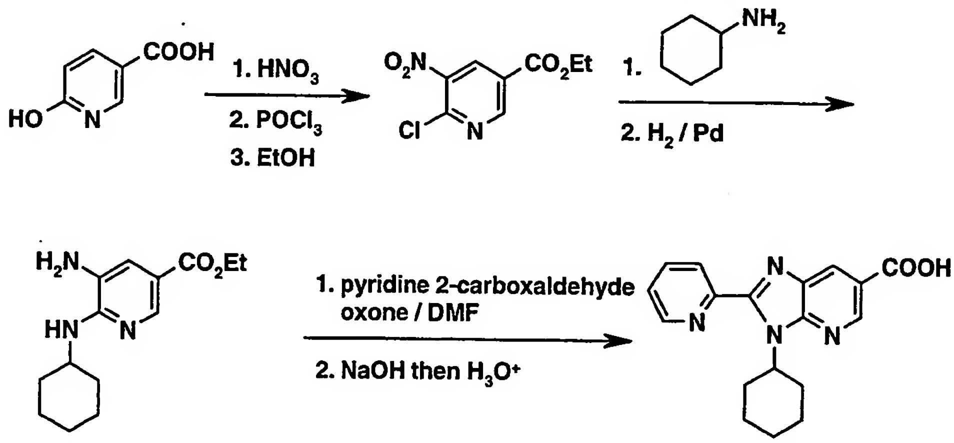
Each well was filled with resin (0.0203 mmol, 35 mg) and was washed with DMF (3 X 1.2 mL). To each well was added a 0.5 M solution of DIEA in DMF (200 µL, 0.1 mmol), a 0.2 M solution of the acid R_1-CO_2H in DMSO (500 µL, 0.1 mmol) and a 0.2 M solution of HATU in DMF (500 µL, 0.1 mmol). The resins were shaken for 6 h at room temperature and the solvent was drained. The coupling was repeated for another 6 h with fresh reagent. The resins were washed successfully with 1.2-mL portions of DMF (3 x), MeOH (3 x), and DCM (3 x).

Cleavage from the resin:

In each well was added 1.0 mL of a 30% solution of TFA/1,2-DCE and the resins were shaken for 1.5 h. The wells were drained and the resins washed once with 2 mL of 1,2-DCE. The resulting filtrates containing 10% TFA in 1,2-DCE was heated at 80 °C for 13 h. The volatiles were removed under vacuum and the residue was lyophilized from MeCN/H_2O to give the crude benzimidazole 5-carboxylic acid derivatives.

EXAMPLE 5:

3-Cyclohexyl-2-pyridin-2-yl-3H-imidazo[4,5-b]pyridine-6-carboxylic acid:



Ethyl 5-amino-6-cyclohexylaminonicotinate:

Ethyl 6-chloro-5-nitronicotinate (1.00 g, 4.33 mmol) prepared according to A. H. Berrie et al. (J. Chem. Soc. 1951, 2590) was dissolved in DMSO (2 mL) and cyclohexylamine (0.54 g, 5.4 mmol) was added. The mixture was stirred for 1 h at room temperature, diluted with water and the yellow precipitate collected by filtration. The product was washed with water and dried (0.95 g, 74% yield).

The nitro derivative from above (0.68 g, 2.32 mmol) was hydrogenated (1 atm H_2) in EtOAc (30 mL) over 5% palladium on charcoal (100 mg). After 2 h, the reaction

(complete by HPLC) was filtered and concentrated under reduced pressure to give the title diamine (0.58 g, 94% yield).

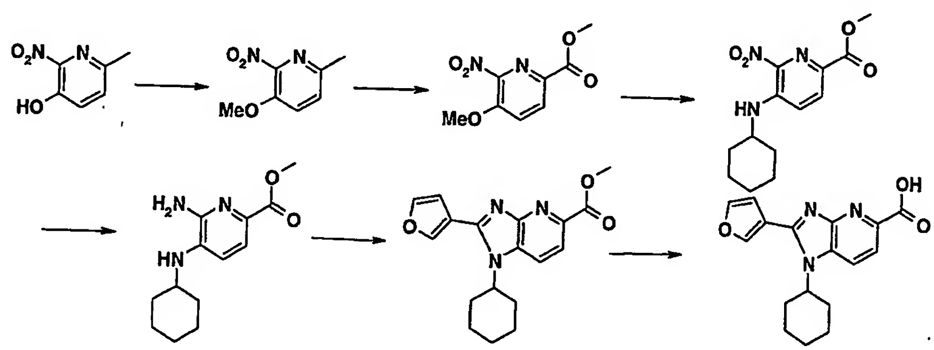
3-Cyclohexyl-2-pyridin-2-yl-3H-imidazo[4,5-b]pyridine-6-carboxylic acid:

The diamine from above (0.58 g, 2.2 mmol) and 2-pyridine carboxaldehyde (0.252 g, 2.4 mmol) were dissolved in a mixture of DMF (2 mL) and water (0.1 mL). Oxone® (1.24 g, 2 mmol) was added and the mixture stirred for 2 h at room temperature. The reaction was diluted with 5% aqueous $NaHCO_3$ and extracted with DCM. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated to a brown oil.

The crude ester was dissolved in MeOH (30 mL) and KOH (300 mg) was added. The mixture was refluxed for 2 h, cooled and concentrated under reduced pressure. The residue was dissolved in water (20 mL) and the solution acidified with 4 N HCl until complete precipitation of the product as a purple solid. The crude product was collected, washed with water, dried, and further purified by preparative HPLC.

EXAMPLE 6:

1-Cyclohexyl-2-furan-3-yl-1H-imidazo[4,5-b]pyridine-5-carboxylic acid:



3-Methoxy-6-methyl-2-nitro-pyridine:

A solution of 3-hydroxy-6-methyl-2-nitropyridine (4.00 g, 26 mmol) in MeOH - DCM (30 mL, 2:1 ratio) was treated with diazomethane in Et_2O until all starting material was converted to 3-methoxy-6-methyl-2-nitropyridine (TLC). The solution was concentrated to dryness to give the desired product as a yellow solid (4.25 g, >98% yield).

5-Methoxy-6-nitro-pyridine-2-carboxylic acid methyl ester:

A solution of 3-methoxy-6-methyl-2-nitro-pyridine (2.25 g, 13.4 mmol) in H_2O containing $MgSO_4$ (5.24 g, 43.7 mmol) was heated to reflux. A solution of $KMnO_4$ (5.72 g, 36.2 mmol) was added slowly over a period of 1 h and reflux was maintained for an additional 5 h. The reaction mixture was cooled to room temperature and concentrated ammonia was added (6 mL). The brown solid was filtered and washed twice with water. The filtrate was concentrated and the new precipitate formed, composed mostly of starting material, was removed by filtration. The filtrate was acidified and extracted twice with EtOAc. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was taken up in MeOH-DCM (40 mL, 1:1 ratio) and a solution of diazomethane in Et_2O was added until a persisting yellow color was observed. The solution was then concentrated to dryness and purified by flash column chromatography, using a gradient of hexane/EtOAc from 6/4 to 4/6 as the eluent, to give 5-methoxy-6-nitro-pyridine-2-carboxylic acid methyl ester (585 mg, 20% yield).

5-Cyclohexylamino-6-nitro-pyridine-2-carboxylic acid methyl ester:

A solution of 5-methoxy-6-nitro-pyridine-2-carboxylic acid methyl ester (0.585 g, 2.75 mmol) and cyclohexylamine (0.636 mL, 5.51 mmol) in DMF (8 mL) was heated at 70 °C for 20 h. The mixture was poured on brine (50 mL) while mixing vigorously. The solid formed was filtered, washed with water and then dissolved in EtOAc. The solution was washed with water, saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give 5-cyclohexylamino-6-nitro-pyridine-2-carboxylic acid methyl ester as a brown oil (0.558 g) which was used in the subsequent step without purification.

6-Amino-5-cyclohexylamino-pyridine-2-carboxylic acid methyl ester:

The crude 5-cyclohexyl-6-nitro-pyridine-2-carboxylic acid methyl ester from above (0.530 g, 1.90 mmol) was stirred in EtOH (10 mL) and 10% Pd/C (50 mg), under 1 atm of H_2 gas at room temperature for 3 days. The suspension was filtered through a pad of celite and concentrated to dryness. The product was purified by flash column chromatography, using a gradient from 60% hexane in EtOAc to 100% EtOAc as the eluent, to give 6-amino-5-cyclohexylamino-pyridine-2-carboxylic acid methyl ester (0.210 g, 30% yield).

1-Cyclohexyl-2-furan-3-yl-1*H*-imidazo[4,5-*b*]pyridine-5-carboxylic acid methyl

ester:

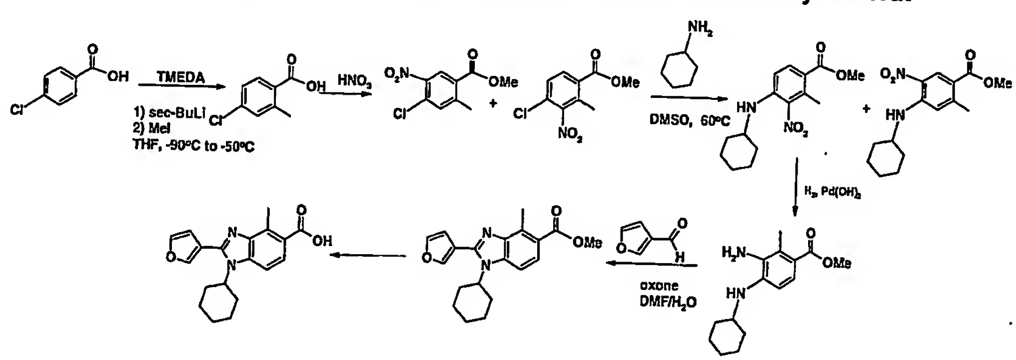
To a solution of the methyl ester from above (0.100 g, 0.40 mmol) in DMF (3 mL) and H_2O (0.300 mL), oxone® (0.813 g, 1.32 mmol) and 3-furaldehyde (0.138 g, 1.32 mmol) were added. The reaction mixture was stirred at room temperature for 5 h and then stored at 5 °C for 3 days. The mixture was diluted with EtOAc and washed twice with water, twice with saturated $NaHCO_3$ and once with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated to give an oil that was purified by flash chromatography, using EtOAc as eluent, to give 1-cyclohexyl-2-furan-3-yl-1H-imidazo[4,5-b]pyridine-5-carboxylic acid methyl ester (0.058 g, 44% yield).

1-Cyclohexyl-2-furan-3-yl-1H-imidazo[4,5-b]pyridine-5-carboxylic acid :

The ester from above (0.058 g, 0.178 mmol) was dissolved in MeOH (2 mL) and aqueous LiOH (0.700 mL, 1 M) was added. The solution was stirred at room temperature for 2 h and then purified by C18 reversed phase preparative HPLC to give the title compound.

Example 7:

1-Cyclohexyl-2-furan-3-yl-4-methyl-1H-benzimidazole-5-carboxylic acid:



4-Chloro-2-methylbenzoic:

In a dry round-bottomed flask (3 L) equipped with a mechanical stirrer under N_2, anhydrous *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 99.7 mL, 660 mmol, 2.2 eq.) and anhydrous THF (600 mL) were added and the mixture was cooled to –90 °C in a bath of liquid N_2/EtOH. Freshly titrated *sec*-BuLi (550 mL, 1.2M in cyclohexane, 660 mmol., 2.2 eq.) was added slowly *via* cannula as to maintain the temperature at –50 °C. The solution was cooled to –90 °C and 4-chlorobenzoic acid (47.0 g in 400 mL anhydrous THF, 300 mmol) was added slowly *via* cannula, while stirring carefully

to maintain the temperature at –90 °C. The reaction mixture was stirred at –90 °C for 1 h before allowed to warm-up to –80 °C and CH_3I (80 mL, 1.28 moles) was added very slowly. The reaction mixture was stirred for 10 min at –80 °C, then quenched slowly with H_2O (600 mL) and allowed to warm-up to room temperature. The aqueous layer was separated, washed with Et_2O (2 x 500 mL) and then acidified with HCl (2.5 N, 600 mL) while cooling in an ice bath; cooling was continued for 16 h at 4°C to allow crystallization of the desired product. The crude product was dried under vacuum and over anhydrous P_2O_5 and then re-crystallized from hot toluene (700 mL) to obtain pure 4-chloro-2-methylbenzoic acid (40 g, 78% yield).

Mixture of 4-chloro-2-methyl-5-nitrobenzoic acid methyl ester and 4-chloro-2-methyl-3-nitrobenzoic acid methyl ester:

These compounds were prepared using a modification of the procedure reported by M. Baumgarth et al. (*J. Med. Chem.* **1997**, *40*, 2017-2034).

4-Chloro-2-methylbenzoic acid (6 g) was added to fuming HNO_3 (100%, 36 g) in small portions over a period of 20 min, at 10 °C, while stirring vigorously. The reaction mixture was stirred vigorously for a period of 1 h and the temperature allowed to warm-up to 20 °C. The reaction mixture was then poured onto ice (100 g) and the yellow precipitate formed was collected, washed with H_2O, dissolved in EtOAc (25 mL) and the solution was dried over Na_2CO_3 and filtered. After concentration of the remaining mother liquor to 1/2 of the original volume, more precipitate was formed, however, the solid formed was always a mixture of 4-chloro-2-methyl-5-nitrobenzoic acid and 4-chloro-2-methyl-3-nitrobenzoic acid. Thus, all of the solid material formed was collected by filtration (~6.5 g), stirred in MeOH/HCl at 0 °C for 1 h to form a mixture of methyl esters. This mixture was used in the following step without further purification.

4-Cyclohexylamino-2-methyl-5-nitrobenzoic acid methyl ester and 4-cyclohexylamino-2-methyl-3-nitrobenzoic acid methyl ester:

The mixture of esters from above (1.1 g, 4.8 mmol) and cyclohexylamine (1.7 mL, 14.4 mmol) in DMSO (2 mL) were stirred at 60 °C for 16 h. The reaction mixture was then cooled and poured onto ice (~5 g) and mixed vigorously to allow the formation of a precipitate. The solid material was filtered, washed with H_2O and dissolved in EtOAc. The solution was washed with H_2O and brine, dried over anhydrous $MgSO_4$ and evaporated to an oil containing the desired products. The oil was triturated with

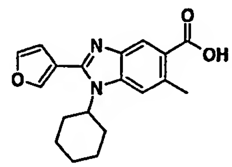
hexane (~5 mL) to allow precipitation of relatively pure 4-cyclohexylamino-2-methyl-5-nitrobenzoic acid methyl ester (600 mg), whereas the mother liquor contained mostly 4-cyclohexylamino-2-methyl-3-nitrobenzoic acid methyl ester (600 mg).

3-Amino-4-cyclohexylamino-2-methylbenzoic acid methyl ester:
4-Cyclohexylamino-2-methyl-3-nitrobenzoic acid methyl ester (150 mg) was dissolved in THF/MeOH (30 mL, 1:2 ratio) and stirred in the presence of H_2 (1 atm) and a catalytic amount of $Pd(OH)_2$ (20 mg) at room temperature for 14 h. The reaction mixture was then filtered, evaporated to dryness and purified by flash column chromatography, using 25% EtOAc in hexane with 0.2% NH_4OH as the eluent, to give the pure aniline (106 mg).

1-Cyclohexyl-2-furan-3-yl-4-methyl-1H-benzimidazole-5-carboxylic acid:
To a solution of the diamine from above (500 mg, 1.9 mmol) in DMF (3 mL) and H_2O (0.15 mL), 3-furaldehyde (0.22 mL, 2.5 mmol) and oxone® (1.29 g, 2.1 mmol) were added and the reaction mixture was stirred at room temperature for 1 h. Subsequently, H_2O (60 mL) was added and the pH was adjusted to 8 with aqueous $NaHCO_3$. The reaction mixture was then extracted with DCM, the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness. The desired benzimidazole methyl ester (446 mg) was obtained pure after column chromatography, using 25% EtOAc in hexane.
Hydrolysis of the methyl ester was achieved with an aqueous solution of NaOH (1.0 N, 0.66 mL, 6.6 mmol) in MeOH/THF (10 mL, 1:1 ratio) at 60 °C for 1.5 h. The reaction mixture was then cooled to room temperature, the pH was adjusted to 4 with AcOH and the organic solvents were evaporated. The remaining aqueous mixture was extracted with DCM (3 x 15 mL) and the combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness to give the desired title compound of example 7, 1-cyclohexyl-2-furan-3-yl-4-methyl-1*H*-benzimidazole-5-carboxylic acid (392 mg, 92% yield).

Example 8:

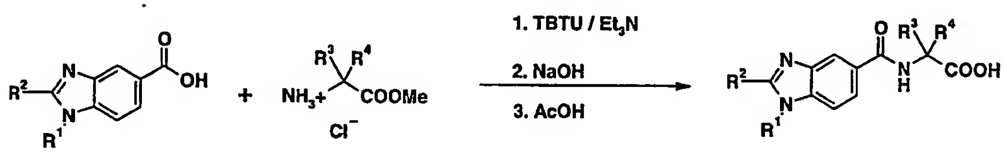
1-Cyclohexyl-2-furan-3-yl-6-methyl-1H-benzimidazole-5-carboxylic acid:



1-Cyclohexyl-2-furan-3-yl-6-methyl-1*H*-benzimidazole-5-carboxylic acid was prepared from 4-cyclohexylamino-2-methyl-5-nitrobenzoic acid methyl ester as described for the 4-methyl derivative in Example 7.

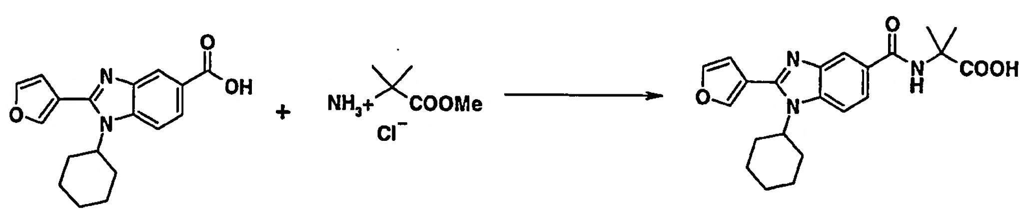
Example 9:

General procedure for coupling amino acid methyl ester hydrochlorides to 5-carboxybenzimidazoles and deprotection of the ester functionality:



5-Carboxybenzimidazole derivatives were coupled to amino ester hydrochlorides under standard amide bond forming conditions (TBTU or HATU and base). The resulting amide esters were then saponified using a metal hydroxide and the desired free carboxylic acid isolated following acidification of the carboxylate salt with AcOH. The procedure is exemplified as follows:

2-{[1-(1-Cyclohexyl-2-furan-3-yl-1*H*-benzoimidazol-5-yl)-methanoyl]-amino}-2-methyl-propionic acid:

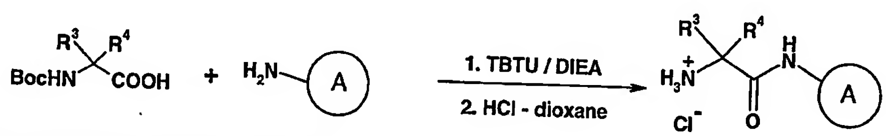


The 5-carboxybenzimidazole derivative (0.125 g, 0.40 mmol) and TBTU (0.154 g, 0.48 mmol) were dissolved in DMSO (1 mL) and Et_3N (280 µL, 2 mmol) was added followed by methyl 2-aminoisobutyrate hydrochloride (0.074 g, 0.48 mmol). The mixture was stirred for 18 h at room temperature or till complete as judged by reversed-phase HPLC analysis. 5N NaOH (1.2 mL, 15 equivalents) was added to

the reaction mixture that was stirred for 4 h at room temperature. The reaction mixture was added drop wise with vigorous stirring to a solution of AcOH (1.5 mL) in water (15 mL). The precipitated solid was collected by filtration, washed with water and dried in vacuo over P_2O_5 giving the title compound (0.129 g).

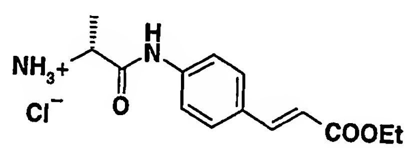
Example 10:

General procedure for the preparation of aromatic amide derivatives from α-monosubstituted N-Boc-amino acids (R^4 = H in Scheme 1):



N-Boc protected α-monosubstituted amino acids were coupled to aromatic amine derivatives using standard amide bond coupling reagents. The *N*-Boc protecting group was then cleaved under acidic conditions and the amine derivatives were isolated as hydrochloride salts. The following procedure for coupling *N*-Boc-D-alanine to ethyl 4-aminocinnamate is representative:

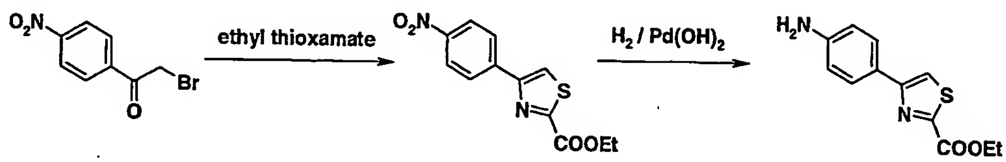
(R)-1-[4-((E)-2-Ethoxycarbonyl-vinyl)-phenylcarbamoyl]-ethyl-ammonium chloride:



N-Boc-D-alanine (0.284 g, 1.5 mmol) was dissolved in DMSO (2 mL) and DIEA (1.04 mL, 6 mmol, 4 equivalents) was added. Ethyl 4-aminocinnamate (0.287 g, 1.5 mmol) was added followed by TBTU (0.578 g, 1.80 mmol) and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with EtOAc (75 mL) and the solution washed with water (40 mL), 1N NaOH (3 x 25 mL), 1M $KHSO_4$ (2 x 25 mL) and 5% $NaHCO_3$ (25 mL). The extract was dried ($MgSO_4$) and concentrated to give the desired *N*-Boc-protected anilide as a yellow solid (0.411 g). The material from above was stirred for 1 h with 4N HCl in dioxane (10 mL). Removal of volatiles under reduced pressure and trituration of the residue with TBME gave the title hydrochloride salt as a brown solid.

Example 11:

4-(4-Amino-phenyl)-thiazole-2-carboxylic acid ethyl ester:

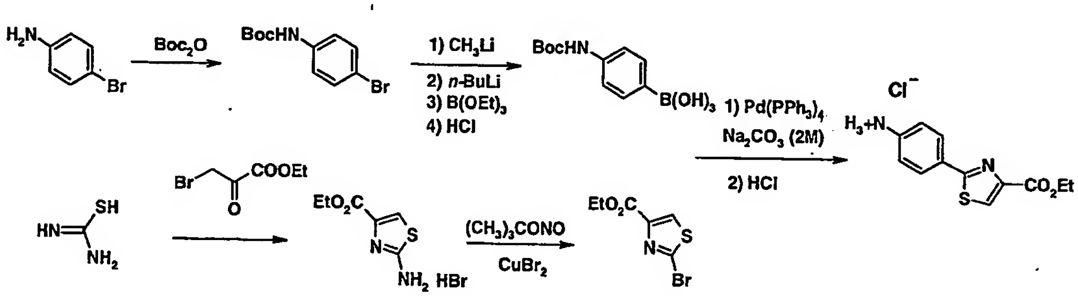


4'-Nitro-2-bromoacetophenone (6.100 g, 25 mmol) and ethyl thioxamate (3.460 g, 26 mmol) were dissolved in MeOH (20 mL) and the solution was refluxed for 1 h. After cooling to room temperature, the precipitated solid was collected by filtration, washed with cold MeOH and dried under vacuum (5.15 g, 75% yield).

A suspension of the nitroester from above (2.50 g, 8.98 mmol) and 20% $Pd(OH)_2$ on carbon (200 mg) in 2:1 EtOH – THF (60 mL) was stirred for 3 h under 1 atm of hydrogen gas. The suspension was filtered to remove the catalyst and volatiles removed under reduced pressure to give the title compound as a reddish foam (2.05 g, 92% yield).

Example 12:

4-(4-Ethoxycarbonyl-thiazol-2-yl)-phenyl-ammonium chloride:



p-Bromoaniline (13.0 g, 76 mmol) and Boc_2O (19.8 g, 91 mmol) were dissolved in toluene (380 mL) and stirred at 70 °C for 15 h. The reaction mixture was cooled to RT, evaporated to dryness, re-dissolved in EtOAc and washed with 0.1M HCl and brine. The organic solution was dried over anhydrous $MgSO_4$, evaporated to dryness and purified by flash column chromatography, using 5% to 10% EtOAc in hexane as the eluent, to obtain the Boc-protected aniline (23 g). The Boc-protected bromoaniline (10.7 g, 39.2 mmol) was dissolved in anhydrous THF (75 mL) in a flask

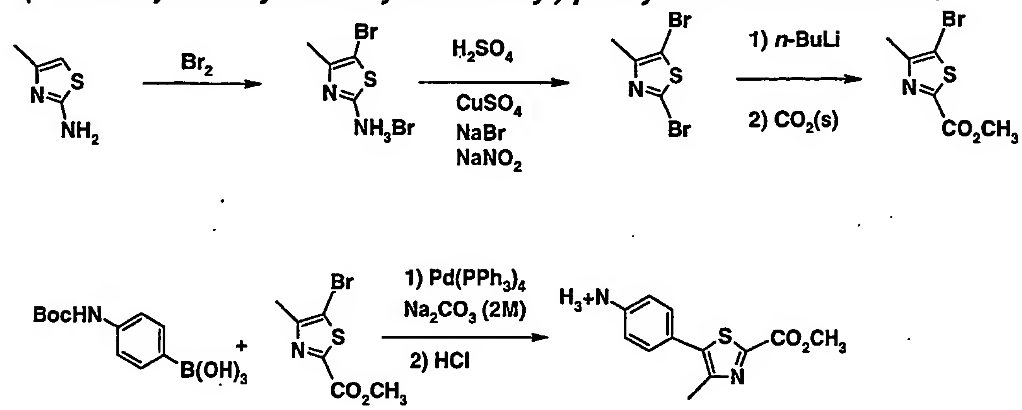
equipped with an overhead stirrer. The solution was cooled to 0 °C and MeLi (1.2 M in Et_2O, 33 mL, 39.2 mmol) was added drop wise while maintaining the internal temperature below 7 °C. The reaction mixture was stirred at 0 °C for 15 min and then cooled to –78 °C before *n*-BuLi (2.4 M in hexane, 17 mL, 39.2 mmol) was added drop wise, maintaining the internal temperature below –70 °C). The reaction mixture was stirred at –78 °C for 1h, $B(OEt)_3$ (17 mL, 98 mmol) was added drop wise (internal temperature < -65 °C) and stirring was continued for 45 min at –78 °C and at 0 °C for 1 h. The reaction mixture was then treated with 5% aqueous HCl (~100 mL, to pH ~1) for 15 min and NaCl(s) was added to saturate the aqueous layer. The aqueous layer was extracted with 0.5 M NaOH (4 x 100 mL) and the combined aqueous layers were acidified with 5% HCl (150 mL, to pH ~1) and extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give the *N*-Boc carbamate of 4-aminophenylboronic acid as a solid (7.5 g).

Thiourea (7.60 g, 100 mmol) and ethyl bromopyruvate (12.6 mL, 100 mmol) were mixed and heated to 100 °C for 45 min. After cooling of the reaction mixture, the solid obtained was triturated with acetone, filtered and recrystallized from EtOH to obtain the desired aminothiazole product (10.6 g, 40 mmol). The aminothiazole was then added slowly (over a period of 20 min) to a solution of *t*-butylnitrite (6.2 g, 60 mmol) and $CuBr_2$ (10.7 g, 48 mmol) in MeCN (160 mL) at 0 °C. The reaction mixture was allowed to warm-up to RT and to stirred for 2.5 h. The mixture was then added to an aqueous HCl solution (20%) and extracted with Et_2O (2 x 400 mL). The organic layer was washed with aqueous HCl (10%), dried over anhydrous $MgSO_4$, and evaporated to dryness. The desired bromothiazole product was isolated in ~85% yield (4.3 g) after flash column chromatography using 15% EtOAc in hexane as the eluent.

To a de-gassed solution of the bromothiazole product (230 mg, 0.97 mmol), the boronic acid derivative from above (230 mg, 0.97 mmol) and aqueous Na_2CO_3 (2M, 3 mL) in DME (3mL), a catalytic amount of $Pd(PPh_3)_4$ (56 mg, 0.049 mmol) was added and the reaction mixture was stirred at 80 °C under argon for 20 h. The reaction mixture was then cooled to RT, diluted with EtOAc and extracted with brine, aqueous $NaHCO_3$ (2 x) and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness. The carbamate-ester product was isolated after flash column chromatography using 20% to 30% EtOAc in hexane: 180 mg. The aniline hydrochloride was isolated after removal of the Boc protecting group with

4N HCl in dioxane for 30 min.

Example 13:
4-(2-Methoxycarbonyl-4-methyl-thiazol-5-yl)-phenyl-ammonium chloride:



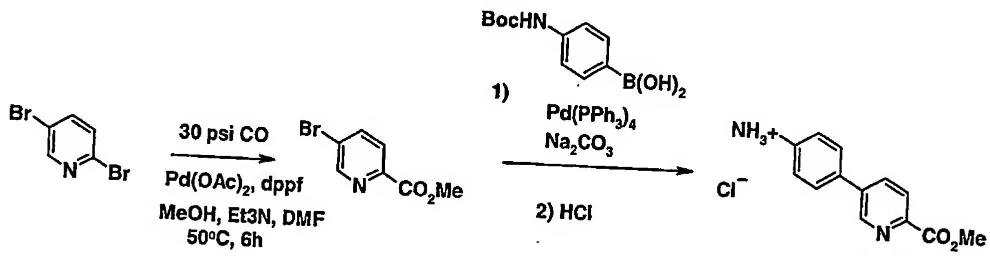
To a solution of 2-amino-4-methylthiazole (7.90 g, 69 mmol) in Et_2O (70 mL) at 15 °C, Br_2 was added slowly over a period of 30 min while stirring vigorously. The solid material formed was filtered and recrystallized from EtOH. The crystalline product was filtered and dried under vacuum to give the 5-bromo derivative as the HBr salt (10.3 g). This product was then dissolved in a solution of $CuSO_4$ (11.4 g) and NaBr (9.9 g) in H_2O (115 mL) and H_2SO_4 (5M, 360 mL) was added at 0 °C. An aqueous solution of $NaNO_2$ (6.10 g in 20 mL of H_2O) was then added drop wise to the reaction mixture over a period of 25 min, maintaining the temperature below 3 °C. The reaction mixture was stirred at 3 °C for 20 min and then at RT for 1 h. The reaction mixture was diluted with brine (280 mL) and extracted with Et_2O (3 x 300 mL). The ether layers were combined, washed with a saturated, aqueous solution of sodium thiosulfate to eliminate any unreacted Br_2, dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel (~200 mL). The solvent was evaporated and the desired product isolated by distillation (bp = 80-81 °C at 15mm Hg).

A solution of the dibromo intermediate (500 mg, 1.94 mmol) in hexane (5 mL) was added to a cooled solution (-70 °C) of *n*-BuLi (870 µL of 2.2M in hexane), diluted with 10 mL of hexane. The reaction was stirred at –70 °C for 1 h and then added to CO_2(s). The mixture was partitioned between H_2O and Et_2O. The aqueous layer was acidified with 1N HCl (pH ~2) and extracted with EtOAc (2 x), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was re-dissolved in MeOH / DCM, treated with CH_2N_2 (until the solution remained yellow) and evaporated to dryness to give the desired 5-bromo-4-methylthiazole-2-carboxylate ester as a yellow solid (230 mg). Suzuki cross-coupling of this product with the *N*-Boc protected 4-

aminophenylboronic acid of example 12, as previously described, gave the building block 5-(4-amino-phenyl)-4-methyl-thiazole-2-carboxylate methyl ester. This product was treated with 4N HCl in dioxane for 30 min to remove the Boc protecting group and obtain the desired compound.

Example 14:

4-(6-Methoxycarbonyl-pyridin-3-yl)-phenyl-ammonium chloride:

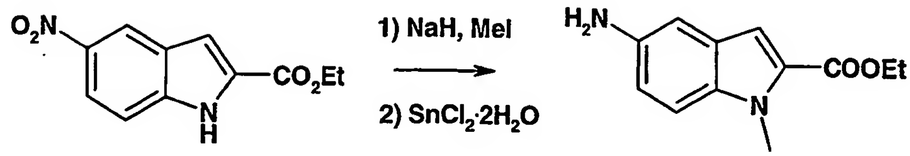


The synthesis of the 5-bromopyridine-2-carboxylic acid methyl ester was achieved following the procedure of Chambers and Marfat (*Synth. Commun.* **1997**, *27*, 515). A solution of 2,5-dibromopyridine (10.0 g, 42.2 mmol), 1,1'-bis(diphenylphosphino)ferrocene (dppf, 1.4 g, 2.5 mmol), $Pd(OAc)_2$ (0.3 g, 1.3 mmol), Et_3N (12 mL, 84 mmol) in dry MeOH (40 mL) and dry DMF (40 mL) was deairated under a stream of CO for 10 min, then shaken in a Parr apparatus under 30 psi CO at 50 °C for 6 h. The mixture was diluted with EtOAc (600 mL) and washed with H_2O (2 x 100 mL), brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated to give a solid. Flash column chromatography, using 20% EtOAc in hexane as the eluent, gave the 5-bromopyridine-2-carboxylic acid methyl ester as a white solid (5.77 g).

Cross-coupling of the 5-bromopyridine-2-carboxylic acid methyl ester with *N*-Boc protected aniline boronic acid (Example 12) under typical Suzuki conditions, followed by removal of the Boc protecting group with HCl (as described previously), afforded the desired compound.

Example 15:

5-Amino-1-methyl-1H-indole-2-carboxylic acid ethyl ester



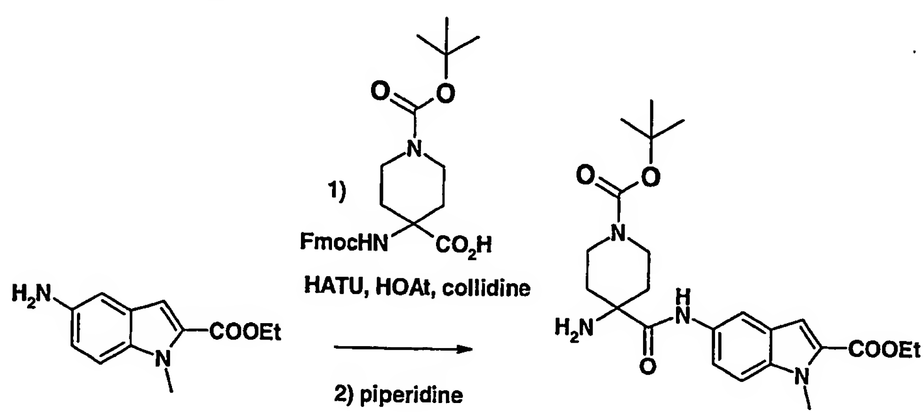
The ethyl ester of 5-nitroindole-2-carboxylic acid (0.300 g, 1.28 mmol) was dissolved in anhydrous DMF (6 mL) and NaH (0.078 g, 60%, 1.92 mmol) was added. The reaction was stirred at RT for 20 min, then MeI (160 μL, 2.56 mmol) was added and stirring was continued for 3 h. The reaction was quenched with the addition of aqueous $NaHCO_3$ (~1%) while stirring vigorously. The brown solid formed (0.096 g) was filtered and dried in air overnight.

The *N*-methyl nitro derivative (196 mg, 0.79 mmol) was then dissolved in DMF (4 mL), H_2O (400 μL) and $SnCl_2 \cdot 2H_2O$ (888 mg, 3.95 mmol) were added, and the mixture was stirred at 60 °C for 3 h. The mixture was then partitioned between 10% aqueous $NaHCO_3$ and EtOAc and stirred vigorously. The aqueous layer was re-extracted with EtOAc and the combined EtOAc layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was purified by flash column chromatography, using 1:1 ratio EtOAc/hexane as the eluent, to obtain the pure 5-aminoindole derivative (118 mg).

N-Alkylation of 5-nitroindole-2-carboxylate with other alkylating agents (such as EtI, propargyl bromide, benzyl bromide) under the conditions described above gave the corresponding 5-amino-1-alkyl-*1H*-indole-2-carboxylates.

Example 16:

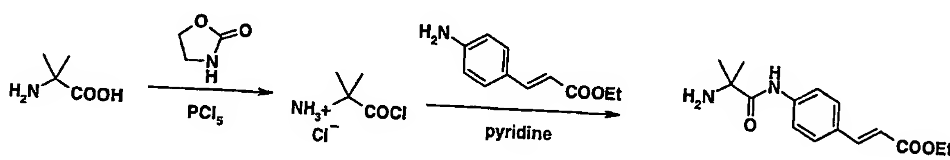
5-{[1-(4-Amino-1-t-butoxycarbonyl-piperidin-4-yl)-methanoyl]-amino}-1-methyl-1H-indole-2-carboxylic acid ethyl ester:



A solution of amino-indole from example 15 (70 mg, 0.32 mmol), *N*-Fmoc-amino-(4-*N*-Boc-piperidinyl)carboxylic acid (150 mg, 0.32 mmol), HATU (139 mg, 0.35 mmol), HOAt (48 mg, 0.35 mmol) and collidine (155 mg, 1.28 mmol) in DMF (2 mL) was stirred at RT for 15 h.. The reaction mixture was diluted with EtOAc, washed with 1% aqueous citric acid (2 x), saturated $NaHCO_3$ (2 x) and brine, dried over anhydrous $MgSO_4$ and concentrated to dryness to give an orange solid (210 mg) which was used in the next reaction without purification. A solution of the crude solid (210 mg) in DMF (3 mL) and piperidine (95 mL, 0.95 mmol) was stirred at RT for 3 h. The reaction mixture was concentrated to dryness and purified by flash column chromatography, using a solvent gradient from 50% EtOAc in hexane to 100% EtOAc as the eluent, to give the desired compound as a brown solid (110 mg).

Example 17:

(E)-3-[4-(2-Amino-2-methyl-propanoylamino)-phenyl]-acrylic acid ethyl ester:



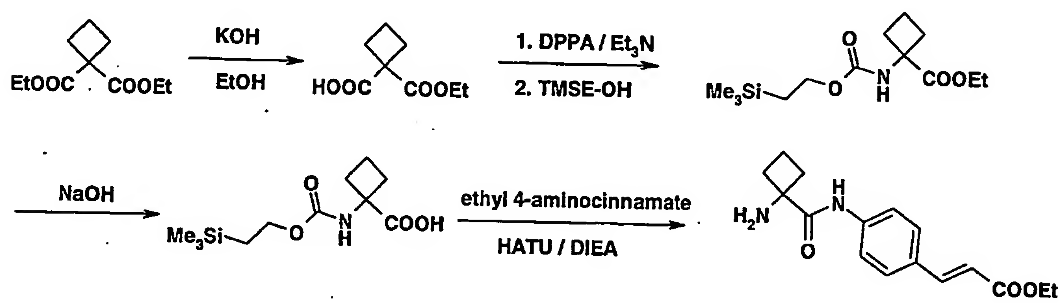
Adapting the procedure described in E. S. Uffelman et al. (*Org. Lett.* **1999**, *1*, 1157), 2-aminoisobutyric acid was converted to the corresponding amino acid chloride hydrochloride: 2-oxazolidinone (12.30 g, 0.141 mole) was dissolved in MeCN (150 mL) and phosphorous pentachloride (49.02 g, 0.235 mole, 1.7 equivalent) was added in one portion. The homogeneous mixture was stirred for 24 h at room temperature. 2-Aminoisobutyric acid (14.55 g, 0.141 mole) was added and the suspension was stirred for 48 h at room temperature. The desired acid chloride hydrochloride was collected by filtration, washed with MeCN and dried under vacuum.

The acid chloride (12.778 g, 80 mmol, 1.4 equivalent) was suspended in DCM (200 mL) and ethyl 4-aminocinnamate (11.045 g, 57.7 mmol, 1 equivalent) was added. Pyridine (7.01 mL, 86.6 mmol, 1.5 equivalent) was added drop wise and the mixture was stirred for 3.5 h at room temperature. The reaction was then poured into a mixture of 1N NaOH (25 mL) and saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc. The organic phase was washed with aqueous $NaHCO_3$, water

and brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure gave the title compound of as a white solid (15.96 g, 101% yield).

Example 18:

(E)-3-(4-{[1-(1-Amino-cyclobutyl)-methanoyl]-amino}-phenyl)-acrylic acid ethyl ester:



Diethyl 1,1-cyclobutanedicarboxylate (20.00 g, 100 mmol) and KOH (6.60 g, 100 mmol) were refluxed in EtOH (100 mL) for 2 h. After cooling to room temperature, volatiles were removed under reduced pressure and the residue partitioned between Et_2O and 4N HCl. The organic extract was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the monoester as a clear oil (14.45 g, 84% yield).

The monoester from above (14.45 g, 84 mmol), Et_3N (14.1 mL, 100 mmol) and diphenylphosphoryl azide (24.05 g, 87.4 mmol) were dissolved in dry toluene (114 mL) and the mixture heated at 80 °C for 1 h and 110 °C for an additional hour. Trimethylsilylethanol (9.94 g, 100 mmol) was added in one portion and the mixture refluxed for 48 h. Toluene was then removed under reduced pressure and the residue dissolved in DCM. The solution was washed with water and brine and dried over $MgSO_4$. Concentration under reduced pressure gave a dark oil which was purified by passage through a pad of silica gel using 30% EtOAc in hexane as eluent. The desired carbamate was obtained as a clear yellow liquid (21.0 g).

The carbamate from above (1.50 g, 5.22 mmol) was dissolved in THF (5 mL) and 2N NaOH (5 mL) was added. The mixture was stirred at 70 °C for 1 h. Following dilution with water, the aqueous phase was washed with Et_2O to remove unreacted starting material. The aqueous phase was then acidified with $KHSO_4$ and the product extracted with EtOAc. The desired free carboxylic acid was obtained as an oil (1.25 g).

The acid from above (0.519 g, 2.0 mmol) was dissolved in DCM (10 mL). DIEA (1.39 mL, 8.0 mmol, 4 equivalents) was added, followed by ethyl 4-aminocinnamate (0.573 g, 3.0 mmol, 1.5 equivalent) and HATU (1.143 g, 3.0 mmol, 1.5 equivalents). The mixture was stirred at room temperature for 3 days. The reaction was poured into TBME (100 mL) and the solution washed successively with 10% aqueous citric acid (2 x 25 mL) and saturated aqueous $NaHCO_3$ (25 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue stirred with TFA (10 mL) for 30 min. Volatiles were then removed under reduced pressure and the residue was co-evaporated twice with hexane. The crude product was dissolved in TBME (60 mL) and the solution washed with 1N NaOH (2 x 25 mL). After drying (Na_2SO_4), volatiles were removed in vacuum to give the title compound as a light brown solid (0.500 g).

Example 19:

Preparation of inhibitors on solid support:

Referring to Scheme 3 above, the following steps were performed on a solid-phase synthesizer (ACT 496 from Advanced Chemtech), using the 96-well reaction block:

Anchoring on the resin:

Each well was filled with bromo Wang resin (0.044 mmol, 40 mg) and was washed with DMF (3 X 1.2 mL). To each well was added DMF (200 µL), a 1 M solution of DIEA in DMF (300 µL, 0.3 mmol), and the appropriate nitro acid derivative (0.176 mmol) dissolved in 500 µL of DMF. The resins were shaken for 15 h at room temperature and the solvent was drained. The resins were washed successively with 1.2 mL portions of DMF (3 x), MeOH (3 x), and DMF (3 x).

Reduction of the nitro group and coupling of Fmoc-amino acids:

The nitro group was reduced to the corresponding aniline using tin (II) chloride dihydrate (1.2 mL of a 0.5 M solution in DMF, 0.6 mmol) for 24 h followed by washing (3 X 1.2 mL) with DMF, DMF/H_2O, DMF, MeOH and DMF. The resin was then suspended in DMF (200 µL) and treated with a 0.5 M solution of DIEA in DMF (300 µL, 0.15 mmol), a 0.13 M solution of Fmoc-amino acid (500 µL, 0.066 mmol) and a 0.13 M solution of TBTU in DMF (500 µL, 0.066 mmol). After shaking for 5 h at 60 °C, and since several reactions were not complete as indicated by the cleavage of a few resin beads, fresh reagents were added and a second coupling was done using

HATU as coupling agent at room temperature for 18 h.

Coupling of the core benzimidazole and cleavage from the resin:

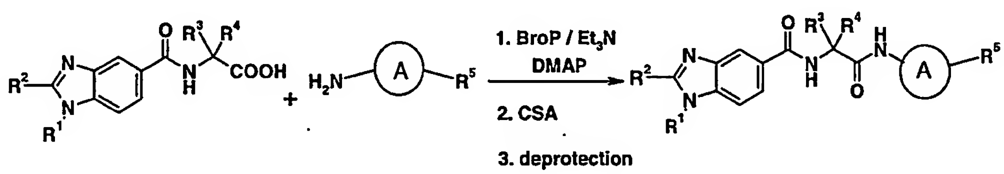
The Fmoc group was cleaved with 20% piperidine/DMF (20 min) and after washing, the 5-carboxybenzimidazole derivative (e.g. from example 1) was coupled under standard conditions using TBTU as coupling agent (room temperature, 18 h).

Cleavage from the resin:

In each well was added 1.0 mL of a 50% solution of TFA/1,2-DCE and the resins were shaken for 1 h. The wells were drained and the resins washed once with 1 mL of the 50% TFA/1,2-DCE solution. The volatiles were removed under vacuum and the compounds were purified by semi-prep reversed phase chromatography to give compounds of formula 1.

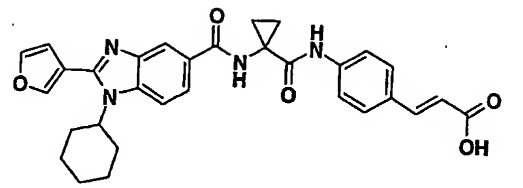
Example 20:

General procedure for coupling N-benzimidazoylamino acids to aromatic amines:



N-Benzimidazoylamino acid derivatives synthesised as described in Example 9 above, were coupled to aromatic amines using BroP / camphor-10-sulfonic acid as coupling agent as described by H. Heimgartner and P. Wipf in *Helv. Chim. Acta*, **1986**, *69*, 1153. Products were deprotected under standard conditions to give compounds of formula 1, which are the subject of the present invention. The following specific Example will serve to illustrate the process and is not intended to be limiting.

(E)-3-(4-{[1-(1-{[1-(1-Cyclohexyl-2-furan-3-yl-1H-benzoimidazol-5-yl)-methanoyl]-amino}-cyclopropyl)-methanoyl]-amino}-phenyl)-acrylic acid (Entry 1070):

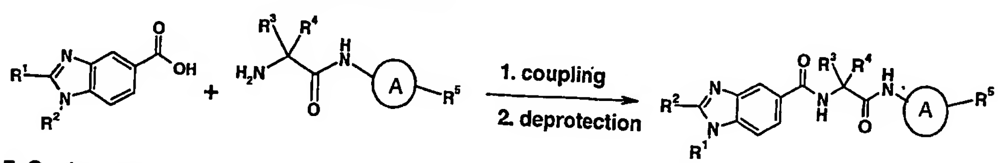


The appropriate amino acid derivative from Example 9 (0.020 g, 0.05 mmol) was dissolved in DCM (1 mL). DMAP (0.018 g, 3 equivalents), Et_3N (20 µL, 0.15 mmol, 3 equivalents), BroP (0.058 g, 0.15 mmol, 3 equivalent), and ethyl-4-aminocinnamate (0.029 g, 0.015 mmol, 3 equivalents) were added and the mixture stirred for 20 h at room temperature. Camphor-10-sulfonic acid (CSA; 0.046 g, 0.2 mmol, 4 equivalents) was added and the reaction mixture was stirred for an additional 24 h at room temperature.

The reaction mixture was then diluted with a 1:1 mixture of EtOAc and Et_2O (5 mL) and extracted with 5% $NaHCO_3$ (1 mL). The mixture was then passed through a cartridge of Extrelut® (EM Science, 0.6 g) to remove water using 1:1 EtOAc:Et_2O as eluent (5 mL). The organic filtrate was concentrated under reduced pressure and the residue co-evaporated with MeCN (5 mL).

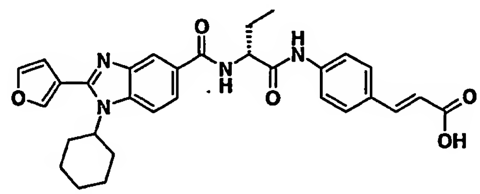
The residue was then dissolved in DMSO (0.8 mL) and 2.5N NaOH (0.2 mL) was added. The mixture was stirred for 2 h at room temperature, neutralized by addition of TFA and the title compound (9 mg) isolated from the reaction mixture by preparative reversed-phase HPLC.

Example 21: General procedure for coupling of α-amino amide derivatives to 5-carboxybenzimidazole derivatives:



5-Carboxybenzimidazole derivatives, such as those described in Examples 1, 3 and 4, were coupled to α-amino amide derivatives, such as those described in Examples 10, 16, 17, and 18, using standard amide bond forming reagents, such as TBTU in the presence of an organic base (DIEA, Et_3N and the like). The resulting products were deprotected under standard conditions (if necessary) to give compounds of formula I, which are the subject of this invention. The following Example is intended to illustrate such a process and is non-limiting.

(E)-3-[4-((R)-2-{[1-(1-Cyclohexyl-2-furan-3-yl-1H-benzoimidazol-5-yl)-methanoyl]-amino}-butanoylamino)-phenyl]-acrylic acid (Entry 1075):



The 5-carboxybenzimidazole derivative (0.020 g, 0.064 mmol) was dissolved in DMSO (0.5 mL). TBTU (0.027 g, 0.084 mmol, 1.3 equivalent) was added followed by Et_3N (36 µL, 0.26 mmol, 4 equivalents). The reaction mixture was stirred for 20 min at room temperature. The amine hydrochloride prepared according to Example 10 (0.029 g, 0.096 mmol, 1.5 equivalent) was added and the mixture stirred for 1 h at room temperature.

DMSO (0.5 mL) and 2.5N NaOH (0.3 mL) were added and stirring at room temperature continued for an additional 1 h. The reaction mixture was then acidified with TFA (0.2 mL) and the title compound was isolated by preparative reversed-phase HPLC.

Example 22: Inhibition of NS5B RNA dependent RNA polymerase activity

The compounds of the invention were tested for inhibitory activity against the hepatitis C virus RNA dependant polymerase (NS5B), according to the following assay:

The substrates are:

a 12 nucleotide RNA oligo-uridylate (or oligo-uridine-monophosphate) (oligo-U) primer modified with biotin at the free 5'C position;

a complementary poly-adenylate (or adenosine monophosphate) (polyA) template of heterogeneous length (1000-10000 nucleotides); and

UTP-[5,6 ^{3}H].

Polymerase activity is measured as the incorporation of UMP-[5,6 ^{3}H] into the chain elongated from the oligo-U primer. The ^{3}H-labelled reaction product is captured by SPA-beads coated with streptavidin and quantified on the TopCount.

All solutions were made from DEPC treated MilliQ water [2 ml of DEPC is added to 1 L of MilliQ water; the mixture is shaken vigorously to dissolve the DEPC, then

autoclaved at 121°C for 30 minutes].

Enzyme: The full length HCV NS5B (**SEQ ID NO.1**) was purified as an N-terminal hexa-histidine fusion protein from baculovirus infected insect cells. The enzyme can be stored at –20°C in storage buffer (see below). Under these conditions, it was found to maintain activity for at least 6 months.

Substrates: The biotinylated oligo-U_{12} primer, the Poly(A) template, and the UTP-[5,6 ^{3}H] were dissolved in water. The solutions can be stored at –80°C.

Assay buffer:
20 mM Tris-HCl pH 7.5
5 mM $MgCl_2$
25 mM KCl
1 mM EDTA
1 mM DTT

NS5B storage buffer:
0.1 µM NS5B
25 mM Tris-HCl pH 7.5
300 mM NaCl
5 mM DTT
1 mM EDTA
0.1 % n-Dodecyl maltoside
30 % glycerol

Test compound cocktail: Just prior to assay, test compounds of the invention were dissolved in assay buffer containing 15% DMSO.

Substrate cocktail: Just prior to assay, the substrates were mixed in assay buffer to the following concentrations:

Component	Concentration in substrate cocktail	Final Concentration in assay
RNAsin™	0.5 U/ µL	1.67 U/ µL
Biotin-oligo-U_{12}	3 ng/µL	1 ng/ µL

primer		
PolyA template	30 ng/ µL	10 ng/ µL
UTP-[5,6-^{3}H] 35 Ci/mmol	0.025 µCi/ µL	0.0083 µCi/ µL 0.25 µM
UTP	2.25 µM	0.75 µM

Enzyme cocktail: Just prior to assay, the RNA polymerase (NS5B) cocktail was prepared in assay buffer to the following specifications:

Component	Concentration in cocktail
Tris-HCl at **pH 7.5**	20 mM
$MgCl_2$	5 mM
KCl	25 mM
EDTA	1 mM
DTT	1 mM
n- Dodecyl maltoside	1%
NS5B	30 nM

Protocol:

The assay reaction was performed in a Microfluor™ white "U" bottom plate (Dynatech™ #7105), by successively adding:

20 µL of test compound cocktail;

20 µL of substrate cocktail; and

20 µL of enzyme cocktail

(final [NS5B] in assay = 10 nM; final [n-dodecyl maltoside] in assay = 0.33%; final DMSO in assay = 5%).

The reaction was incubated at room temperature for 1.5 hours. STOP solution (20 µL; 0.5 M EDTA, 150 ng/ µl tRNA) was added, followed by 30 µl streptavidin coated PVT beads (8mg/ml in 20 mM Tris-HCl, pH 7.5, 25 mM KCl, 0.025% NaN_3). The plate was then shaken for 30 minutes. A solution of CsCl was added (70 µL, 5 M), to bring the CsCl concentration to 1.95 M. The mixture was then allowed to stand for 1 hour. The beads were then counted on a Hewlett Packard TopCount™ instrument using the following protocol:

Data mode: counts per minute

Scintillator: liq/plast
Energy range: low
Efficiency mode: normal
Region: 0-50
Count delay: 5 minutes
Count time: 1 minute
Expected results: 6000 cpm/well
200 cpm/well no enzyme control.

Based on the results at ten different concentrations of test compound, standard concentration-% inhibition curves were plotted and analysed to determine IC_{50}'s for the compounds of the invention. For some compounds, the IC_{50} was estimated from two points.

Example 23: Specificity of NS5B RNA dependent RNA polymerase inhibition

Some of the compounds of the invention were tested for inhibitory activity against polio virus RNA dependent RNA polymerase and the polio virus in the format that is described for the HCV polymerase with the exception that polio virus polymerase was used in place of the HCV NS5B polymerase. Select compounds were also tested for inhibitor of the calf thymus DNA-dependent RNA polymerase II (Kim and Dahimus, 1998, J. Biol. Chem. 263, 18880-18885).

Example 24: Cell Based HCV RNA Replication Assay

Cell Culture

Huh7 cells that stably maintain a subgenomic HCV replicon were established as previously described (Lohman et al., 1999. Science **285**: 110-113) and designated as the S22.3 cell-line. S22.3 cells were maintained in Dulbecco's Modified Earle Medium (DMEM) supplemented with 10% FBS and 0.5 mg/mL neomycin (Standard Medium). During the assay, DMEM medium supplemented with 10% FBS, containing 0.5% DMSO and lacking neomycin was used (Assay Medium). 16 hours prior to compound addition, S22.3 cells are trypsinized and diluted to 100 000 cells/ml in Standard Medium. 100µL (10 000 cells) are distributed into each well of a 96-well plate. The plate was then incubated at 37°C with 5% CO_2 until the next day.

Reagents and Materials:

Product	Company	Catalog #	Storage
DMEM	Wisent Inc.	10013CV	4°C
DMSO	Sigma	D-2650	RT
Dulbecco's PBS	Gibco-BRL	14190-136	RT
Fetal Bovine Serum	Bio-Whittaker	14-901F	-20°C/4°C
Neomycin (G418)	Gibco-BRL	10131-027	-20°C/4°C
Trypsin-EDTA	Gibco-BRL	25300-054	-20°C/4°C
96-well plates	Costar	3997	RT
PVDF 0.22µm Filter Unit	Millipore	SLGV025LS	RT
Deep-Well Titer Plate Polypropylene	Beckman	267007	RT

Preparation of Test Compound

10µL of test compound (in 100% DMSO) was added to 2 ml of Assay Medium for a final DMSO concentration of 0.5% and the solution was sonicated for 15 min and filtered through a 0.22µM Millipore Filter Unit. 900µl was transferred into row A of a Polypropylene Deep-Well Titer Plate. Rows B to H, contain 400µL aliquots of Assay Medium (containing 0.5% DMSO), and were used to prepare serial dilutions (1/2) by transferring 400µl from row to row (no compound was included in row H).

Application of test compound to cells

Cell culture medium was aspirated from the 96-well plate containing the S22.3 cells. 175µL of assay medium with the appropriate dilution of test compound was transferred from each well of the compound plate to the corresponding well of the cell culture plate (row H was used as the "No inhibition control"). The cell culture plate was incubated at 37°C with 5% CO_2 for 72 hours.

Extraction of Total Cellular RNA

Following the 72 hour incubation period, the total cellular RNA was extracted from the S22.3 cells of the 96-well plate using the RNeasy 96 kit (Qiagen®, RNeasy Handbook. 1999.). Briefly, assay medium was completely removed from cells and 100 µL of RLT buffer (Qiagen®) containing 143 mM β-mercaptoethanol was added to each well of the 96-well cell-culture plate. The microplate was gently shaken for 20 sec. 100 µL of 70% ethanol was then added to each microplate well, and mixed by

pipetting. The lysate was removed and applied to the wells of a RNeasy 96 (Qiagen®) plate that was placed on top of a Qiagen® Square-Well Block. The RNeasy 96 plate was sealed with tape and the Square-Well Block with the RNeasy 96 plate was loaded into the holder and placed in a rotor bucket of a 4K15C centrifuge. The sample was centrifuged at 6000 rpm (~5600 x g) for 4 min at room temperature. The tape was removed from the plate and 0.8 ml of Buffer RW1 (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The RNeasy 96 plate was placed on top of another clean Square-Well Block, the tape removed and 0.8 ml of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The tape was removed and another 0.8 ml of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 10 min at room temperature. Tape was removed, the RNeasy 96 plate was placed on top of a rack containing 1.2-mL collection microtubes. The RNA was eluted by adding 50 µL of RNase-free water to each well, sealing plate with a new piece of tape and incubated for 1 min at room temperature. The plate was then centrifuged at 6000 rpm for 4 min at room temperature. The elution step was repeated with a second volume of 50 µl RNase-free water. The microtubes with total cellular RNA are stored at –70°C.

Quantification of Total Cellular RNA

RNA was quantified on the STORM® system (Molecular Dynamics®) using the RiboGreen® RNA Quantification Kit (Molecular Probes®). Briefly, the RiboGreen reagent was diluted 200-fold in TE (10mM Tris-HCl pH =7.5, 1mM EDTA). Generally, 50µL of reagent was diluted in 10mL TE. A Standard Curve of ribosomal RNA was diluted in TE to 2µg/mL and pre-determined amounts (100, 50, 40, 20, 10, 5, 2 and 0µL) of the ribosomal RNA solution were then transferred to a new 96-well plate (COSTAR # 3997) and the volume was completed to 100µL with TE. Generally, column 1 of the 96-well plate was used for the standard curve and the other wells were used for the RNA samples to be quantified. 10µL of each RNA sample that was to be quantified, was transferred to the corresponding well of the 96-well plate and 90µL of TE was added. One volume (100µL) of diluted RiboGreen reagent was

added to each well of the 96-well plate and incubated for 2 to 5 minutes at room temperature, protected from light (a 10 µL RNA sample in a 200 uL final volume generates a 20 X dilution). The fluorescence intensity of each well was measured on the STORM® system (Molecular Dynamics®). A standard curve was created on the basis of the known quantities of the ribosomal RNA and the resulting fluorescent intensities. The RNA concentration in the experimental samples was determined from the standard curve and corrected for the 20X dilution.

Reagents and Materials:

Product	Company	Catalog #	Storage
DEPC	Sigma	D5758	4°C
EDTA	Sigma	E5134	RT
Trizma-Base	Sigma	T8524	RT
Trizma-HCl	Sigma	T7149	RT
Collection Tube Strips	Qiagen	19562	RT
Ribogreen RNA Quantitation Kit	Molecular Probe	R11490	-20°C
Rneasy 96 Kit	Qiagen	74183	RT
Square-Well Blocks	Qiagen	19573	RT

Real-Time RT-PCR

The Real-Time RT-PCR was performed on the ABI Prism 7700 Sequence Detection System using the TaqMan EZ RT-PCR Kit from (Perkin-Elmer Applied Biosystems®). RT-PCR was optimized for the quantification of the 5' IRES of HCV RNA by using the Taqman technology (Roche Molecular Diagnostics Systems) similar to the technique previously described (Martell et al., 1999. J. Clin. Microbiol. 37: 327-332). The system exploits the 5'-3' nucleolytic activity of AmpliTaq DNA polymerase. Briefly, the method utilizes a dual-labeled fluorogenic hybridization probe (**SEQ ID NO. 4**) that specifically anneals to the template between the PCR primers (**SEQ ID NO. 2** and **SEQ ID NO. 3**). The 5' end of the probe contains a fluorescent reporter (6-carboxyfluorescein [FAM]) and the 3' end contains a fluorescent quencher (6-carboxytetramethylrhodamine [TAMRA]). The FAM reporter's emission spectrum was suppressed by the quencher on the intact hybridization probe. Nuclease degradation of the hybridization probe releases the

reporter, resulting in an increase in fluorescence emission. The ABI Prism 7700 sequence detector measures the increase in fluorescence emission continuously during the PCR amplification such that the amplified product was directly proportional to the signal. An amplification plot represents the logarithmic phase of product accumulation and a point representing a defined detection threshold of the increase in the fluorescent signal associated with the exponential growth of the PCR product for the sequence detector was defined as the cycle threshold (C_T). C_T values are inversely proportional to the quantity of input HCV RNA; such that under identical PCR conditions, the larger the starting concentration of HCV RNA, the lower the C_T. A standard curve was created automatically by the ABI Prism 7700 detection system by plotting the C_T against each standard dilution of known HCV RNA concentration. Reference samples for the standard curve are included on each RT-PCR plate. HCV Replicon RNA was synthesized (by T7 transcription) *in vitro*, purified and quantified by OD_{260}. Considering that 1μg of this RNA = 2.15 X 10^{11} RNA copies, dilutions are made in order to have 10^8, 10^7, 10^6, 10^5, 10^4, 10^3 or 10^2 genomic RNA copies / 5μL. Total cellular Huh-7 RNA was also incorporated with each dilution (50ng / 5μL). 5μL of each reference standard (HCV Replicon + Huh-7 RNA) was combined with 45μL of Reagent Mix, and used in the Real-Time RT-PCR reaction.

The Real-Time RT-PCR reaction was set-up for the experimental samples that were purified on RNeasy 96 –well plates by combining 5μl of each total cellular RNA sample with 45μL of Reagent Mix.

Reagents and Materials:

Product	Company	Catalog #	Storage
TaqMan EZ RT-PCR Kit	PE Applied Biosystems	N808-0236	-20°C
MicroAmp Optical Caps	PE Applied Biosystems	N801-0935	RT
MicroAmp Optical 96-Well Reaction Plate	PE Applied Biosystems	N801-0560	RT

Reagent Mix preparation:

Component	Volume for one sample (μL)	Volume for One Plate (μL) (91 samples + Dead Volume)	Final conc.
Rnase-free water	16.5	1617	

5X TaqMan EZ buffer	10	980	1X
$Mn(OAc)_2$ (25mM)	6	588	3mM
dATP (10mM)	1.5	147	300µM
dCTP (10mM)	1.5	147	300µM
dGTP (10mM)	1.5	147	300µM
dUTP (20mM)	1.5	147	600µM
Forward Primer (10µM)	1	98	200nM
Reverse Primer (10µM)	1	98	200nM
PUTR probe (5µM)	2	196	200nM
rTth DNA polymerase (2.5 U/µL)	2	196	0.1 U/µL
AmpErase UNG (1U/µL)	0.5	49	0.01 U/µL
Total Volume	45	4410	

Forward Primer Sequence (SEQ ID NO. 2): 5' - ACG CAG AAA GCG TCT AGC CAT GGC GTT AGT - 3'

Reverse Primer Sequence (SEQ ID NO. 3): 5' - TCC CGG GGC ACT CGC AAG CAC CCT ATC AGG - 3'

Note: Those primers amplify a region of 256-nt present within the 5' untranslated region of HCV.

PUTR Probe Sequence (SEQ ID NO. 4): 6FAM - TGG TCT GCG GAA CCG GTG AGT ACA CC - TAMRA

No Template Controls (NTC): On each plate, 4 wells are used as "NTC". For these controls, 5µl of water are added to the well in place of RNA.

Thermal Cycling Conditions:

50°C 2 min

60°C 30 min

95°C 5 min

$$\left.\begin{array}{ll} 95°C & 15\text{ sec} \\ 60°C & 1\text{ min} \end{array}\right\} \text{for 2 cycles}$$

$$\left.\begin{array}{ll} 90°C & 15\text{ sec} \\ 60°C & 1\text{ min} \end{array}\right\} \text{for 40 cycles}$$

Following the termination of the RT-PCR reaction the data analysis requires setting of threshold fluorescence signal for the PCR plate and a standard curve was constructed by plotting the Ct value versus RNA copy number used in each reference reaction. The Ct values obtained for the assay samples were used to interpolate an RNA copy number based on the standard curve.
Finally, the RNA copy number was normalized (based on the RiboGreen RNA quantification of the total RNA extracted from the cell culture well) and expressed as genome equivalents / µg of total RNA [ge/µg].

The RNA copy number [g.e./µg] from each well of the cell culture plate was a measure of the amount of replicating HCV RNA in the presence of various concentrations of inhibitor. The % inhibition was calculated with the following equation:

[100 – ([g.e./µg] inh / [g.e./µg] ctl)x 100].

A non-linear curve fit with the Hill model was applied to the inhibition-concentration data, and the 50% effective concentration (EC_{50}) was calculated by the use of SAS software (Statistical Software System; SAS Institute, Inc. Cary, N.C.).

Table of compounds

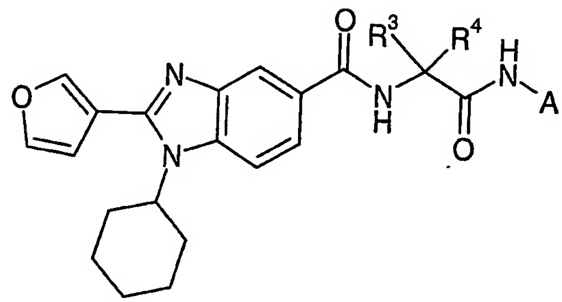
The compounds listed in Tables 1 to 3 were found to be active in the above-described NS5B assay (described in Example 22), with IC_{50}'s of less than 25 µM. None of these compounds were found to exhibit significant inhibition of poliovirus RNA dependent RNA polymerase or calf thymus DNA dependent RNA polymerase II (of Example 23) at 25µM concentration. The compounds were also active in the cell-based assay, with EC_{50}'s of less than 50µM.

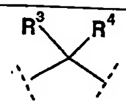
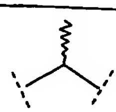
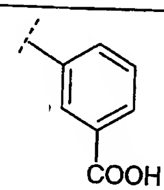
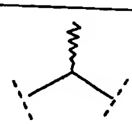
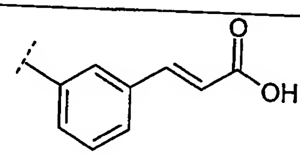
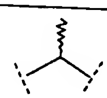
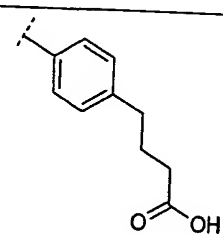
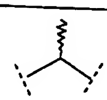
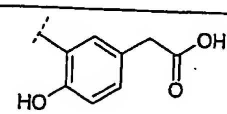
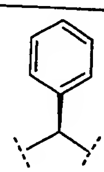
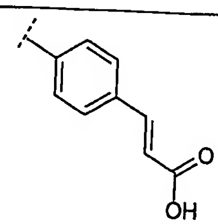
In the Tables 1 to 3, the following ranges apply:

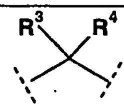
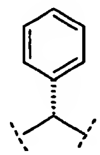
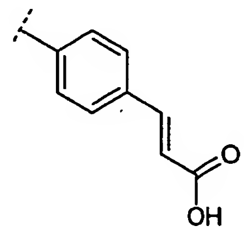
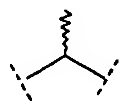
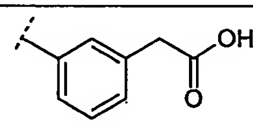
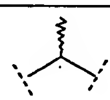
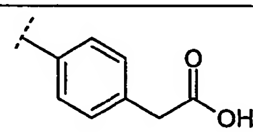
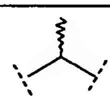
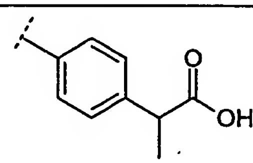
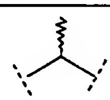
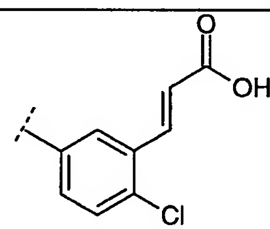
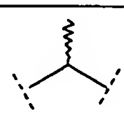
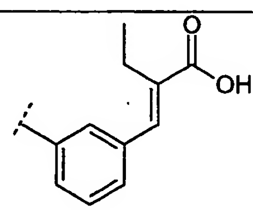
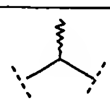
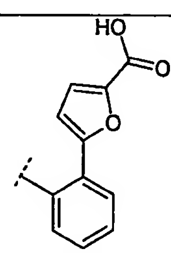
For IC_{50} A = 25μM-5μM; B = 5-0.5μM; and C = <0.5μM

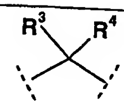
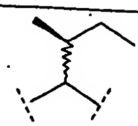
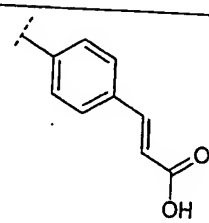
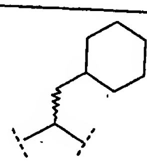
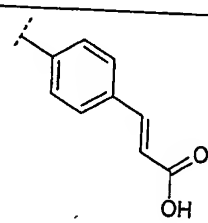
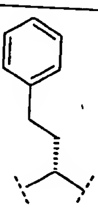
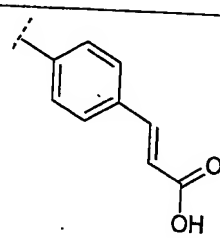
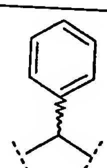
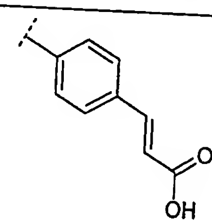
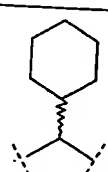
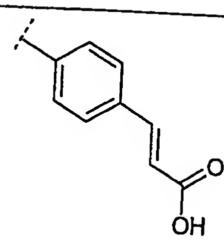
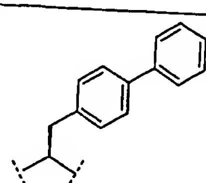
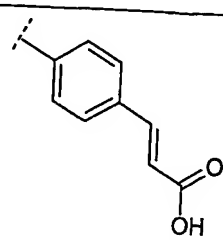
For EC_{50} A = 50μM-5μM; and B = ≤5μM

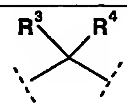
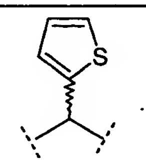
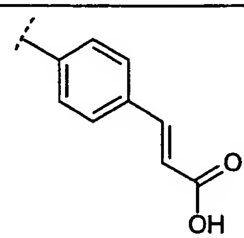
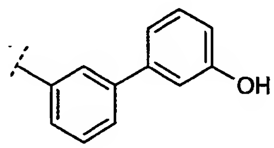
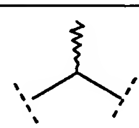
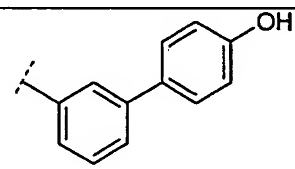
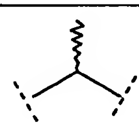
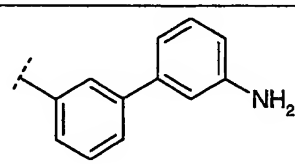
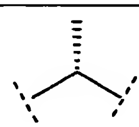
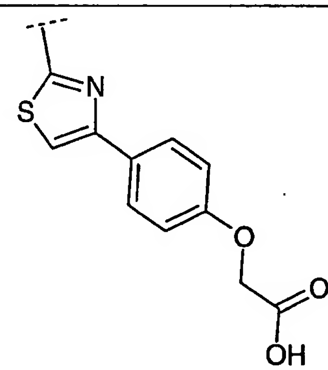
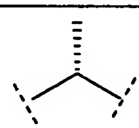
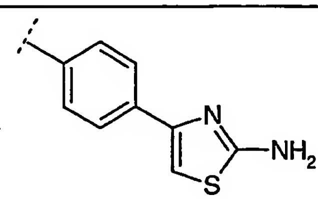
TABLE 1

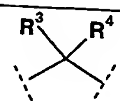
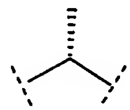
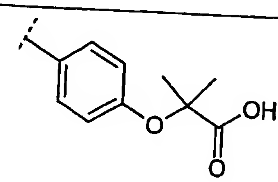
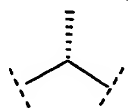
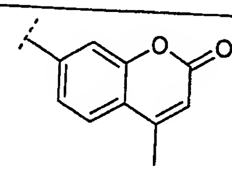
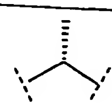
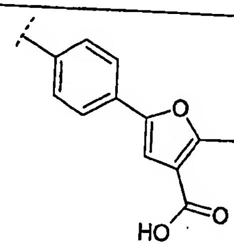
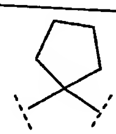
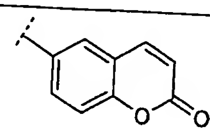
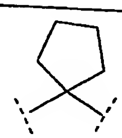
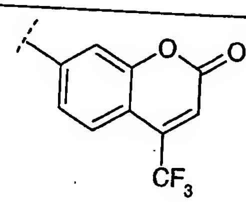
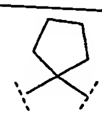
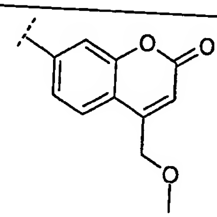
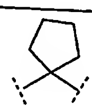
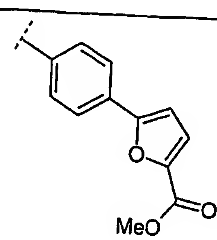


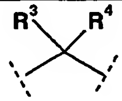
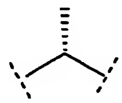
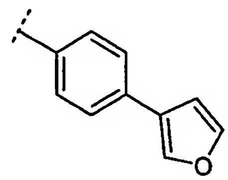
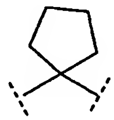
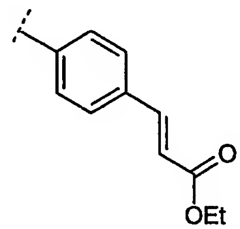
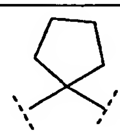
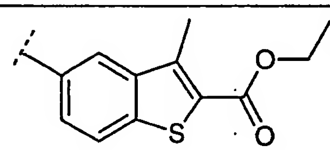
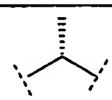
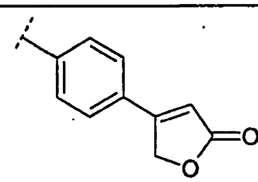
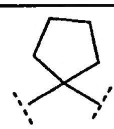
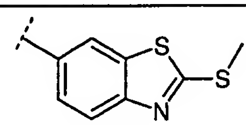
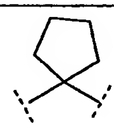
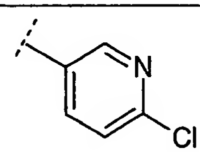
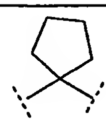
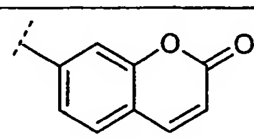
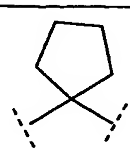
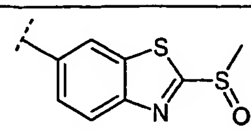
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1001			B	--	501.1
1002			B	--	527.2
1003			B	--	543.2
1004			B	--	531.2
1005			B	--	589.3

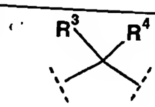
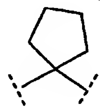
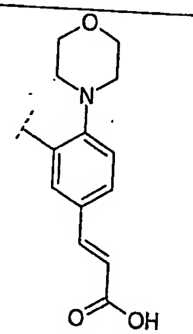
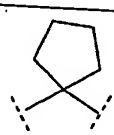
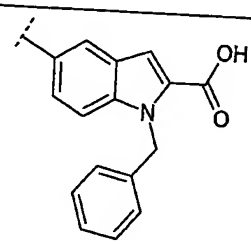
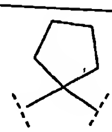
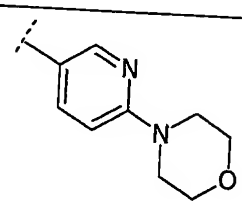
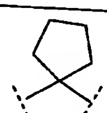
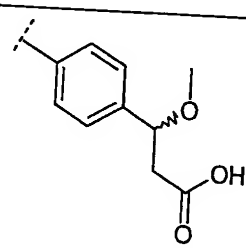
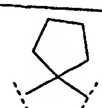
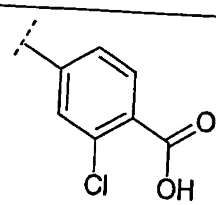
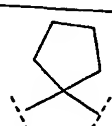
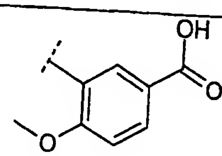
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1006			B	--	589.3
1007			B	--	515.3
1008			B	--	515.3
1009			B	--	529.3
1010			B	--	562.1
1011			B	--	555.2
1012			B	--	567.2

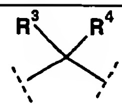
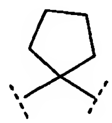
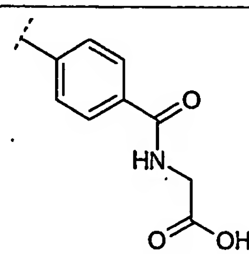
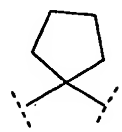
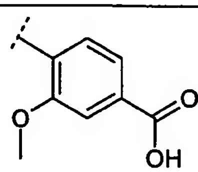
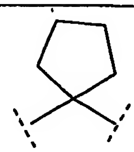
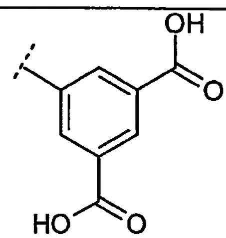
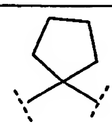
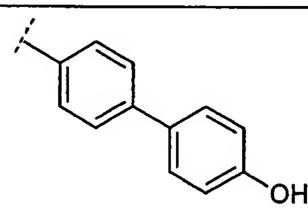
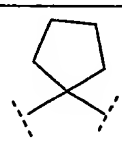
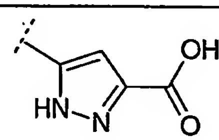
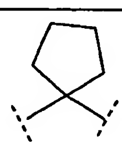
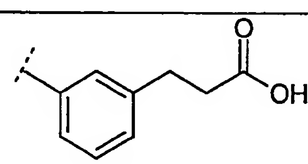
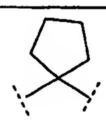
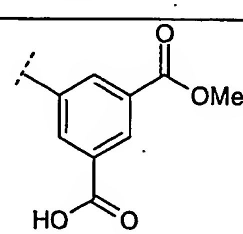
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^{+}$
1013			B	--	569.3
1014			B	--	609.2
1015			B	--	617.2
1016			B	--	589.3
1017			B	--	595.2
1018			A	--	679.3

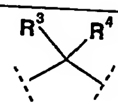
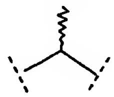
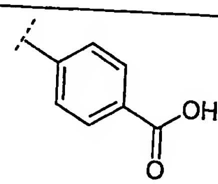
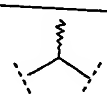
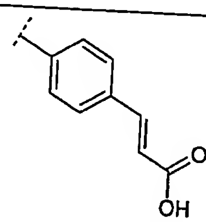
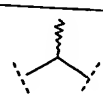
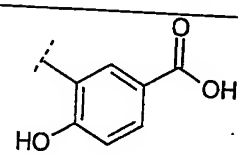
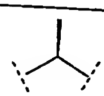
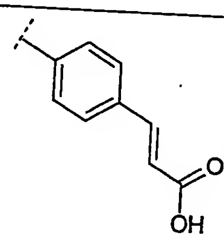
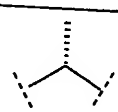
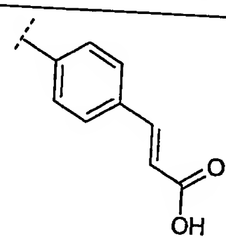
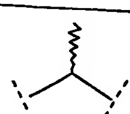
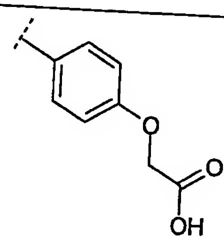
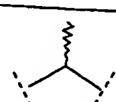
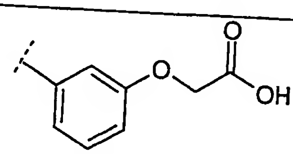
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1019			B	--	595.2
1020			A	--	549.2
1021			A	--	549.2
1022			B	A	548.2
1023			B	--	614.2
1024			B	--	555.2

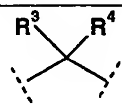
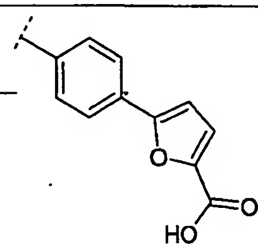
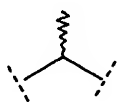
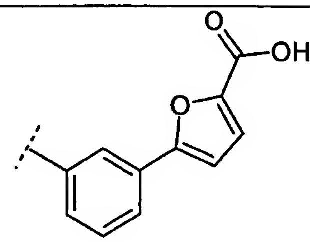
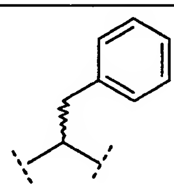
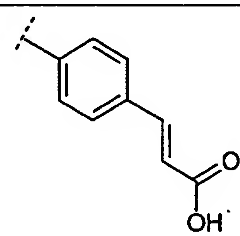
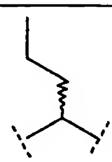
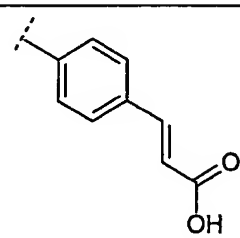
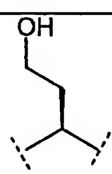
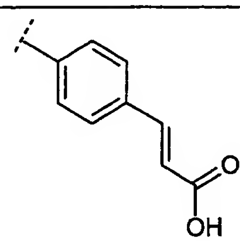
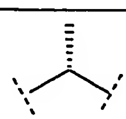
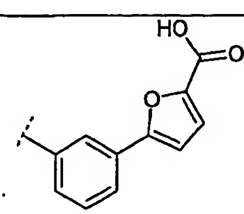
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1025			B	--	559.2
1026			B	B	539.2
1027			B	--	581.2
1028			B	--	565.2
1029			A	--	633.2
1030			B	--	609.2
1031			B	--	621.2

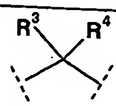
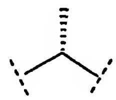
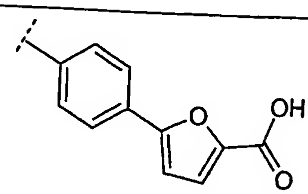
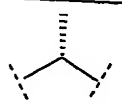
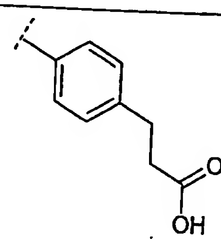
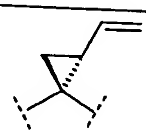
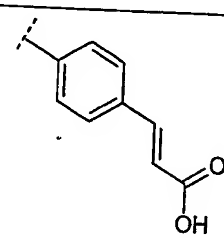
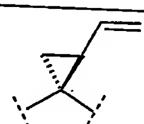
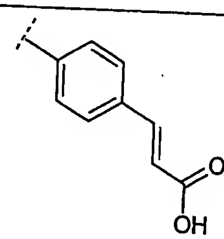
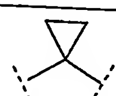
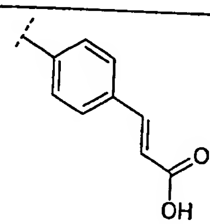
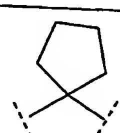
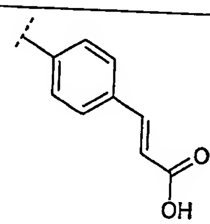
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1032			B	--	523.2
1033			A	--	595.2
1034			B	--	639.2
1035			B	--	539.2
1036			B	--	600.2
1037			B	--	532.2
1038			B	--	565.2
1039			B	--	616.2

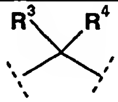
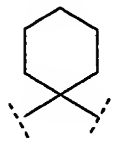
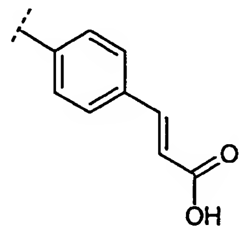
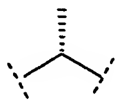
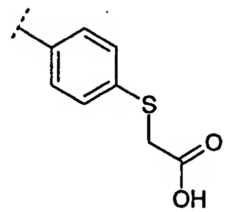
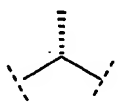
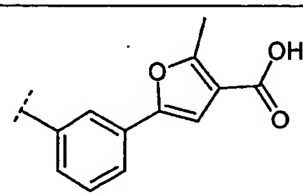
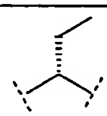
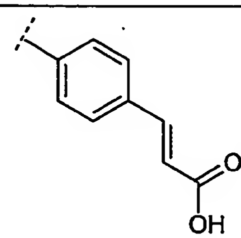
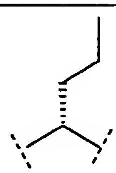
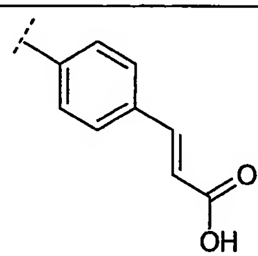
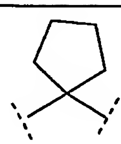
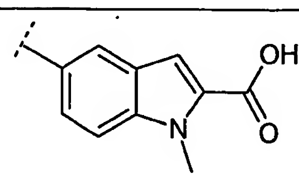
Cpd. #		A	IC_{50}	EC_{50}	m/z (M+H)$^+$
1040			A	--	652.3
1041			B	--	670.3
1042			B	--	583.3
1043			B	--	599.3
1044			B	--	575.2
1045			B	--	571.2

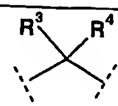
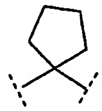
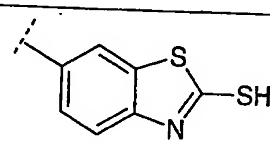
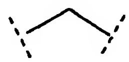
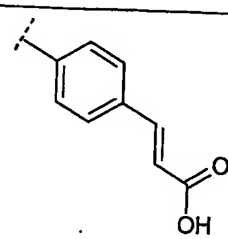
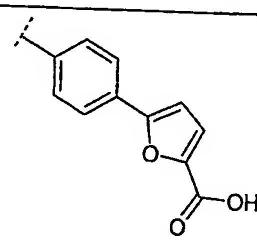
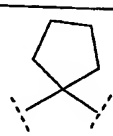
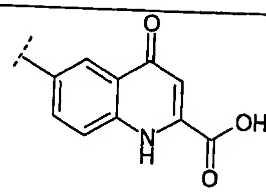
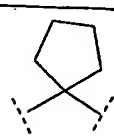
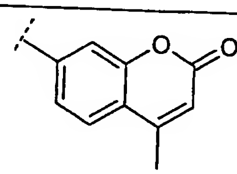
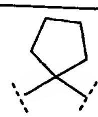
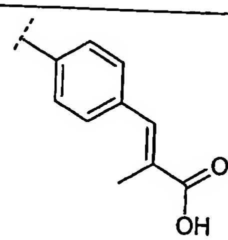
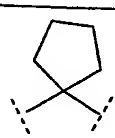
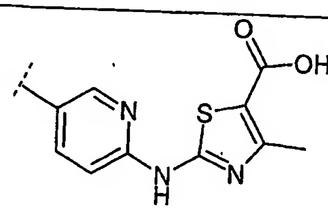
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1046			B	--	598.2
1047			B	--	571.2
1048			B	--	585.2
1049			B	--	589.3
1050			B	--	531.2
1051			B	--	569.2
1052			B	--	599.2

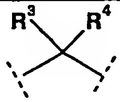
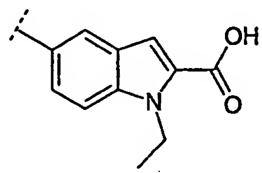
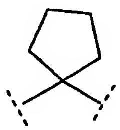
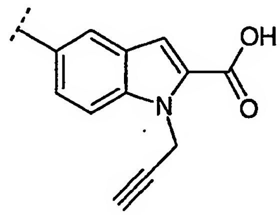
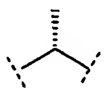
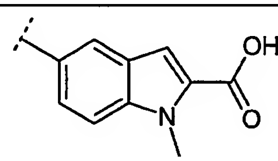
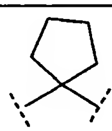
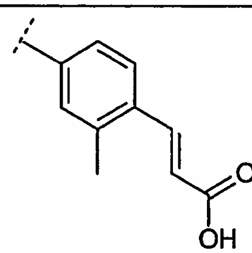
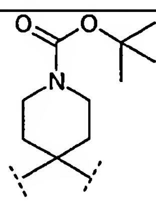
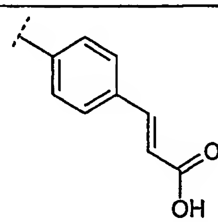
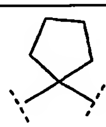
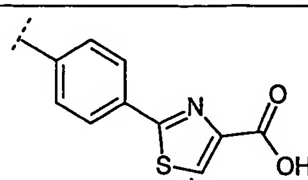
Cpd. #		A	IC50	EC50	m/z (M+H)+
1053			B	A	501.1
1054			C	A	527.2
1055			B	--	517.2
1056			C	A	527.2
1057			C	A	527.2
1058			B	--	531.2
1059			B	--	531.2

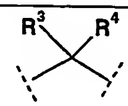
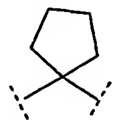
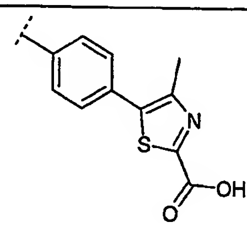
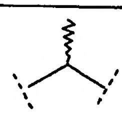
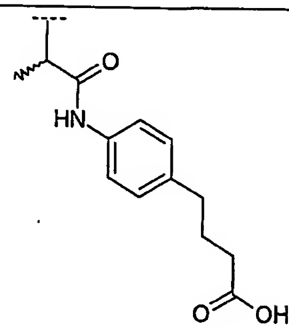
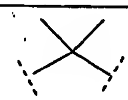
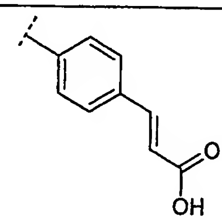
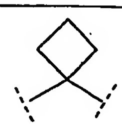
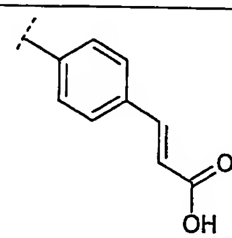
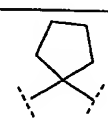
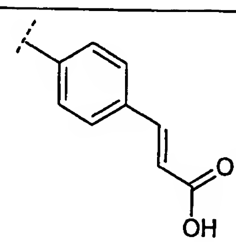
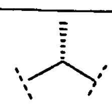
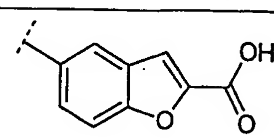
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1060			C	A	567.2
1061			C	--	567.2
1062			B	--	603.3
1063			C	--	555.2
1064			B	--	557.3
1065			C	--	567.2

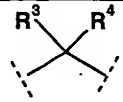
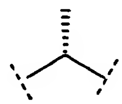
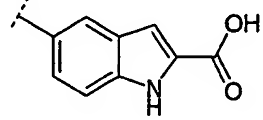
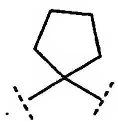
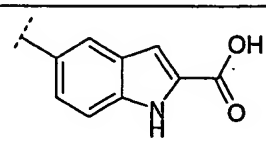
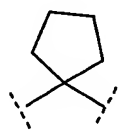
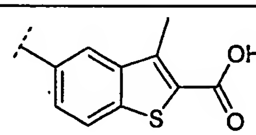
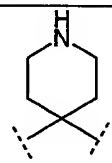
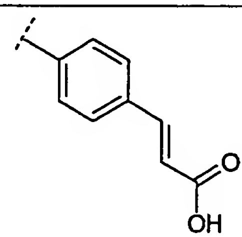
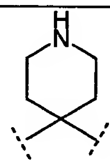
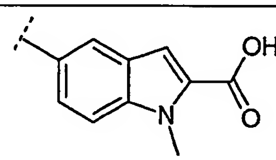
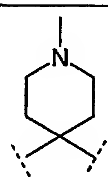
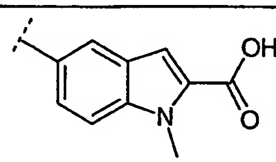
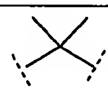
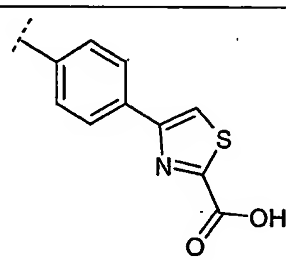
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1066			C	--	567.2
1067			B	--	529.2
1068			C	B	565.2
1069			C	B	565.3
1070			C	A	539.2
1071			C	B	567.3

Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1072			C	B	581.2
1073			B	--	547.2
1074			B	B	581.2
1075			C	A	541.3
1076			B	B	555.3
1077			C	B	594.3

Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1078			B	B	586.1
1079			C	A	513.1
1080			C	B	607.2
1081			C	--	608.2
1082			B	--	579.3
1083			C	B	581.3
1084			B	--	654.3

Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1085			C	B	608.3
1086			C	--	618.2
1087			C	--	554.3
1088			C	B	581.3
1089			C	B	682.3
1090			C	--	624.2

Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1091			B	B	638.2
1092			A	--	614.3
1093			C	B	541.2
1094			C	B	553.2
1095			C	B	567.3
1096			C	--	541.2

Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1097			C	--	540.2
1098			C	A	580.3
1099			C	B	611.2
1100			C	B	582.3
1101			C	--	609.3
1102			C	--	623.2
1103			C	--	598.2

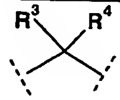
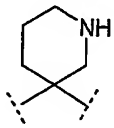
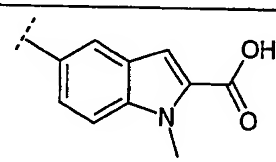
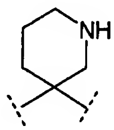
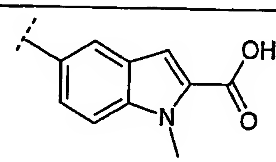
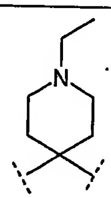
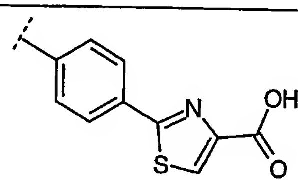
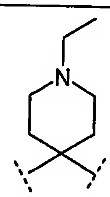
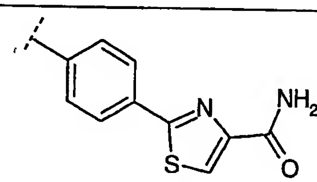
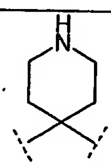
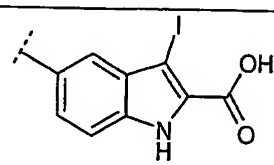
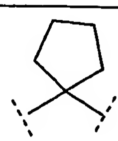
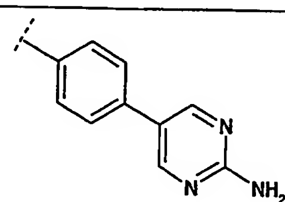
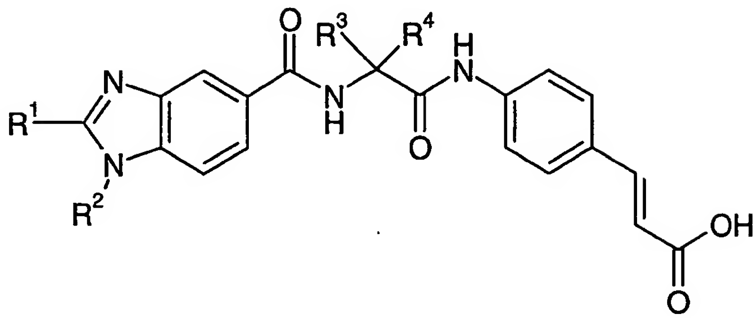
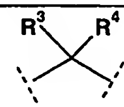
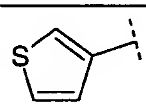
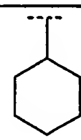
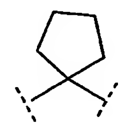
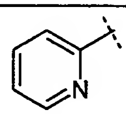
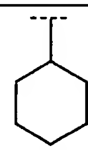
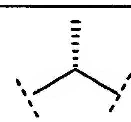
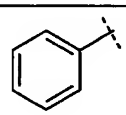
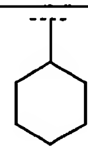
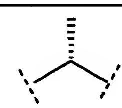
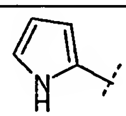
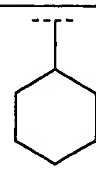
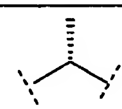
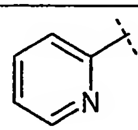
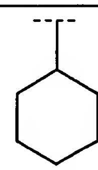
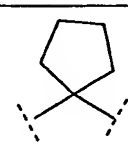
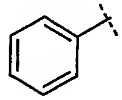
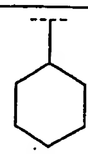
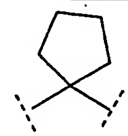
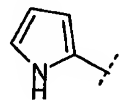
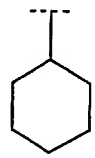
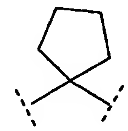
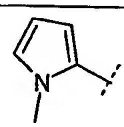
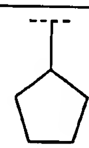
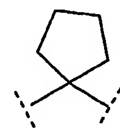
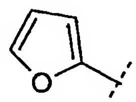
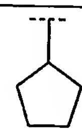
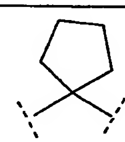
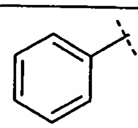
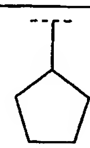
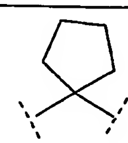
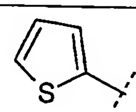
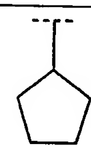
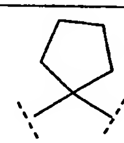
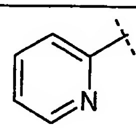
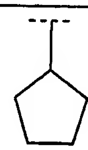
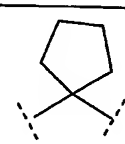
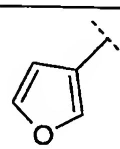
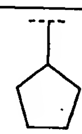
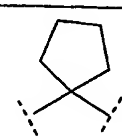
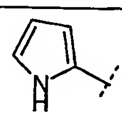
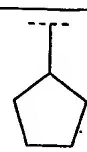
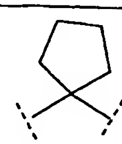
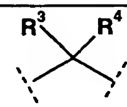
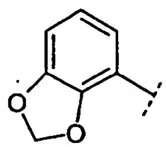
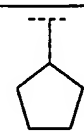
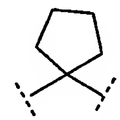
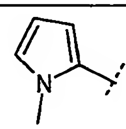
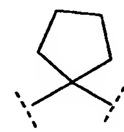
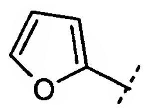
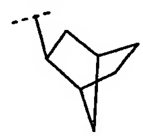
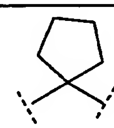
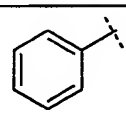
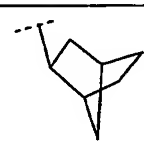
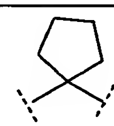
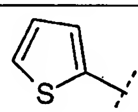
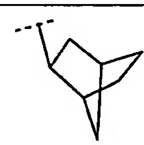
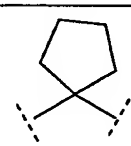
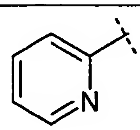
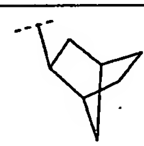
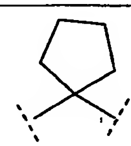
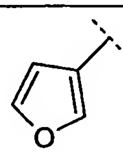
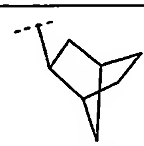
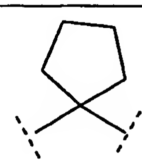
Cpd. #		A	IC_{50}	EC_{50}	m/z $(M+H)^+$
1104	 (+) enantiomer		B	B	609.3
1105	 (-) enantiomer		C	B	609.3
1108			C	B	667.3
1109			C	B	666.3
1110			C	--	721.2
1111			B	--	590.4

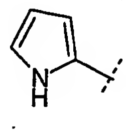
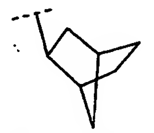
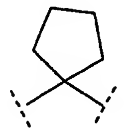
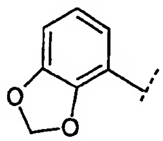
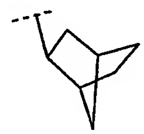
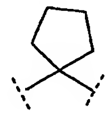
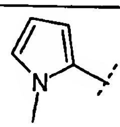
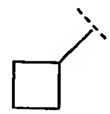
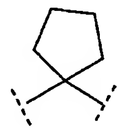
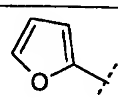
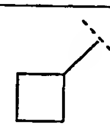
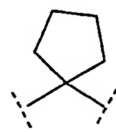
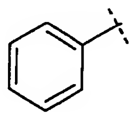
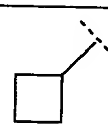
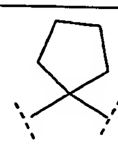
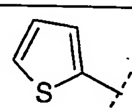
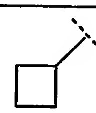
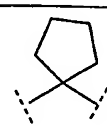
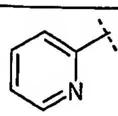
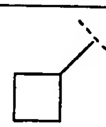
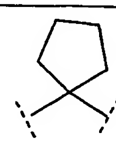
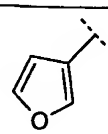
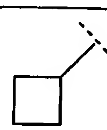
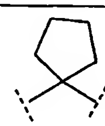
TABLE 2

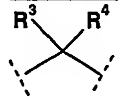
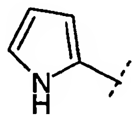
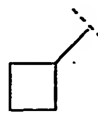
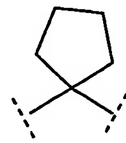
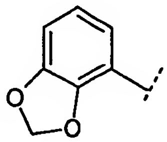
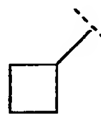
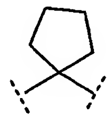
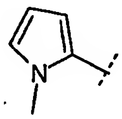
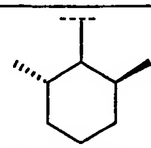
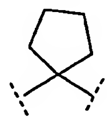
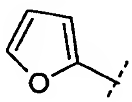
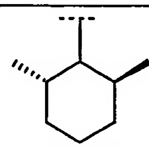
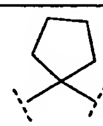
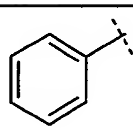
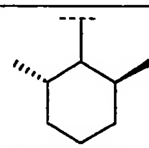
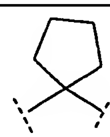
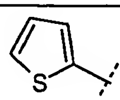
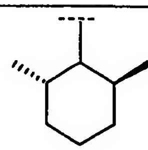
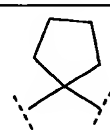
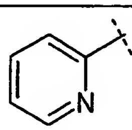
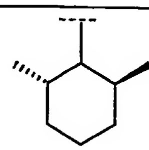
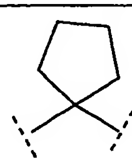


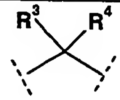
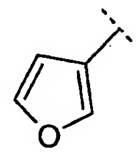
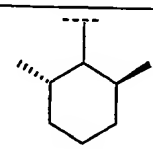
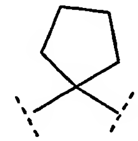
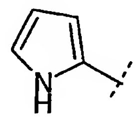
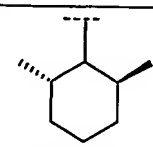
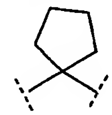
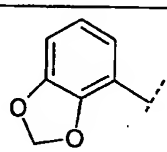
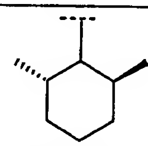
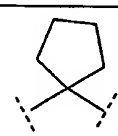
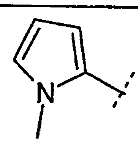
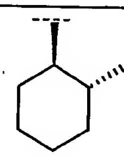
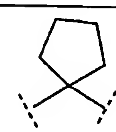
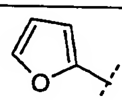
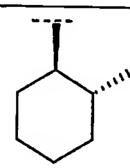
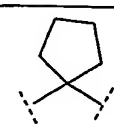
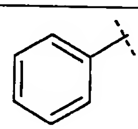
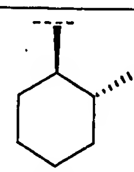
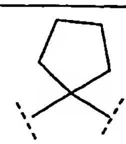
Cpd. #	R^1	R^2		IC_{50}	EC_{50}	m/z $(M+H)^+$
2001				C	B	583.2
2002				C	B	538.3
2003				B	A	537.2
2004				C	A	526.2
2005				C	B	578.3

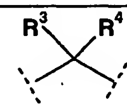
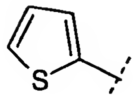
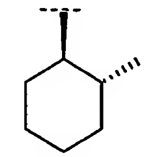
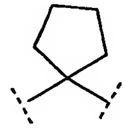
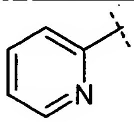
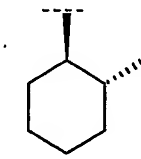
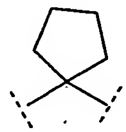
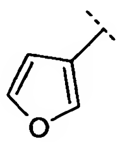
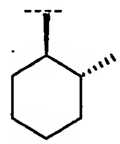
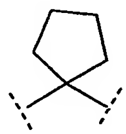
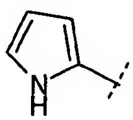
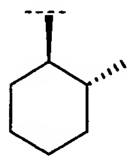
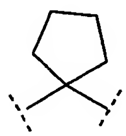
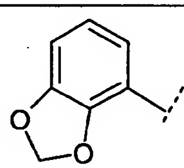
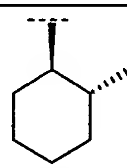
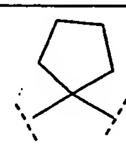
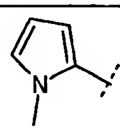
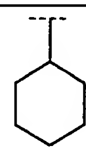
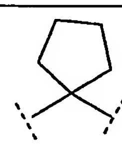
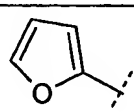
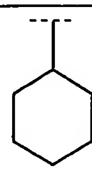
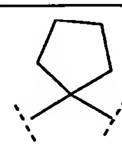
Cpd. #	R^1	R^2	R^3 R^4 	IC_{50}	EC_{50}	m/z $(M+H)^+$
2006				B	B	577.3
2007				C	B	566.3
2008				B	--	566.3
2009				B	--	553.2
2010				B	--	563.3
2011				B	--	569.2
2012				B	A	564.3
2013				C	A	553.2
2014				B	--	552.2

Cpd. #	R^1	R^2		IC_{50}	EC_{50}	m/z $(M+H)^+$
2015				B	--	607.2
2016		 Racemic mixture		B	--	592.3
2017		 Racemic mixture		C	B	579.3
2018		 Racemic mixture		B	--	589.3
2019		 Racemic mixture		C	B	595.2
2020		 Racemic mixture		C	B	590.3
2021		 Racemic mixture		C	B	579.3

Cpd. #	R^1	R^2	R^3 R^4	IC_{50}	EC_{50}	m/z $(M+H)^+$
2022		 Racemic mixture		B	--	578.3
2023		 Racemic mixture		B	--	633.3
2024				B	--	552.3
2025				B	--	539.2
2026				B	--	549.3
2027				B	--	555.2
2028				B	--	550.3
2029				B	--	539.2

Cpd. #	R^1	R^2	R^3 R^4 	IC_{50}	EC_{50}	m/z $(M+H)^+$
2030				B	--	538.3
2031				B	--	593.2
2032		 Mixture of enantiome diastereoisomers		B	--	608.3
2033		 Mixture of enantiome diastereoisomers		B	B	595.3
2034		 Mixture of enantiome diastereoisomers		B	--	605.3
2035		 Mixture of enantiome diastereoisomers		C	B	611.3
2036		 Mixture of enantiome diastereoisomers		B	B	606.3

Cpd. #	R^1	R^2		IC_{50}	EC_{50}	m/z $(M+H)^+$
2037		 Mixture of enantiome diastereoisomers		B	B	595.3
2038		 Mixture of enantiome diastereoisomers		B	--	594.3
2039		 Mixture of enantiome diastereoisomers		B	--	649.3
2040		 Racemic mixture		B	--	594.3
2041		 Racemic mixture		B	--	581.3
2042		 Racemic mixture		B	--	591.3

Cpd. #	R^1	R^2		IC_{50}	EC_{50}	m/z $(M+H)^+$
2043		 Racemic mixture		B	--	597.3
2044		 Racemic mixture		B	B	592.3
2045		 Racemic mixture		B	B	581.3
2046		 Racemic mixture		B	--	580.3
2047		 Racemic mixture		B	--	635.3
2048				C	B	580.3
2049				C	B	567.3

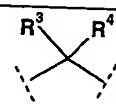
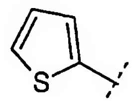
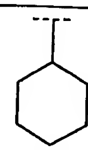
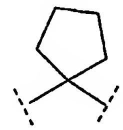
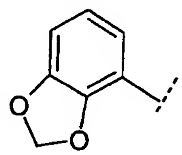
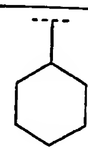
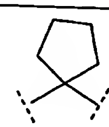
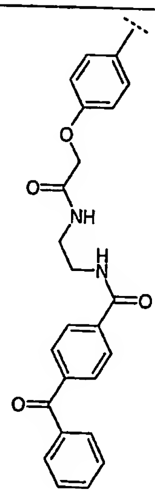
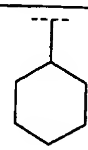
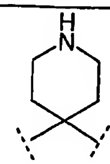
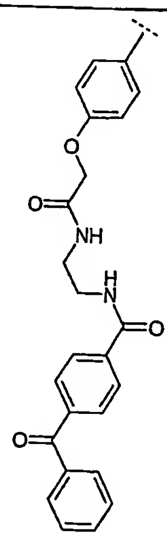
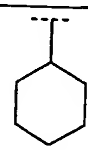
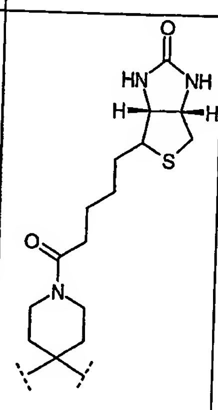
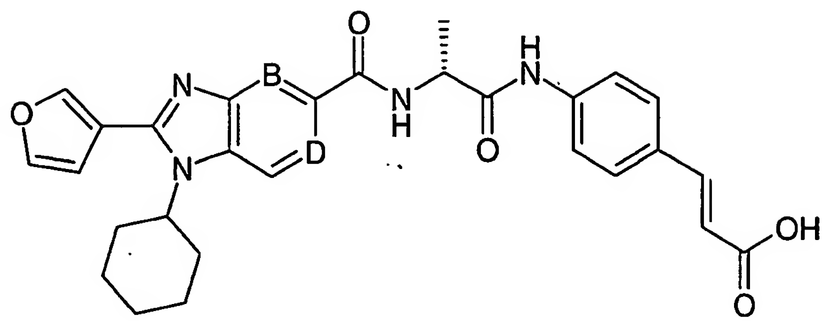
Cpd. #	R^1	R^2		IC_{50}	EC_{50}	m/z $(M+H)^+$
2050				C	B	583.3
2051				B	--	621.3
2052				A	--	917
2053				A	--	1142.4

TABLE 3

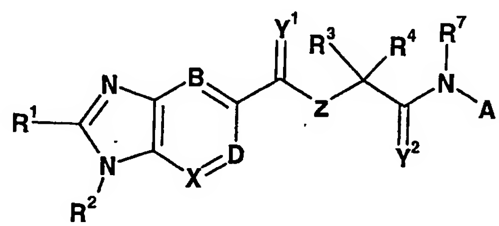


Compound entry #	B	D	IC_{50}	EC_{50}	$m/z(M+H)^+$
3001	N	CH	C	A	528.2
3002	CH	CMe	B	--	541.2
3003	CMe	CH	B	A	541.2

CLAIMS

WE CLAIM:

1. An isomer, enantiomer, diastereoisomer, or tautomer of a compound, represented by formula I:



I

wherein

R^1 is selected from: **R^{11}**, O**R^{11}**, S**R^{11}**, COO**R^{11}**, $SO_2N(R^{12})_2$, $N(R^{12})_2$, , CON(R^{12})$_2$, NR^{12}C(O)R^{12} or NR^{12}C(O)NR^{12} wherein **R^{11}** and each **R^{12}** is independently H, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{2-6})alkynyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, said **R^{11}** and **R^{12}** being optionally substituted with **R^{10}**; or both **R^{12}** are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

R^2 is selected from (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**,

said alkyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, **Het**, alkyl-aryl and alkyl-**Het** being optionally substituted with from 1 to 4 substituents selected from: halogen, or

a) (C_{1-6})alkyl optionally substituted with:

- O**R^{21}** or S**R^{21}** wherein **R^{21}** is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or

- N(**R^{22}**)$_2$ wherein each **R^{22}** is independently H, (C_{1-6})alkyl, (C_{3-}

$_{7})$cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both $\mathbf{R^{22}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

b) OR^{23} wherein $\mathbf{R^{23}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**;

c) SR^{24} wherein $\mathbf{R^{24}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; and

d) $N(\mathbf{R^{25}})_2$ wherein each $\mathbf{R^{25}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both $\mathbf{R^{25}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

B is N or CR^5, wherein $\mathbf{R^5}$ is H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or $\mathbf{R^5}$ is OR^{51} or SR^{51}, COR^{51} or $NR^{51}COR^{51}$ wherein each $\mathbf{R^{51}}$ is independently H, (C_{1-6})alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or $\mathbf{R^5}$ is $NR^{52}R^{53}$ wherein $\mathbf{R^{52}}$ and $\mathbf{R^{53}}$ are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or both $\mathbf{R^{52}}$ and $\mathbf{R^{53}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

X is N or CR^5, wherein $\mathbf{R^5}$ is as defined above;

D is N or CR^5, wherein $\mathbf{R^5}$ is as defined above;

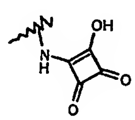
each of $\mathbf{Y_1}$ and $\mathbf{Y_2}$ is independently O or S;

Z is O, N, or NR^6 wherein $\mathbf{R^6}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

R^3 and R^4 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** are optionally substituted with R^{30}; or R^7 and R^8 are covalently bonded together to form second (C_{3-7})cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when **Z** is NR^6, either of R^7 or R^8 is covalently bonded to R^6 to form a nitrogen-containing 5-or 6-membered heterocycle;

R^7 is H, $(C_{1-6}$ alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**, all of which optionally substituted with R^{70}; or R^7 is covalently bonded to either of R^3 or R^4 to form a 5- or 6-membered heterocycle;

A is a 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, (C_{1-6}) alkyl-CONH-aryl or (C_{1-6}) alkyl-CONH-**Het**, all of which being optionally substituted with:



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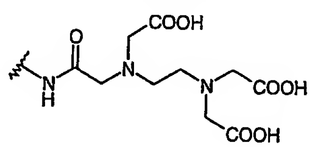


, or R^{100};

or a salt or a derivative thereof;

wherein **Het** is defined as:

5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicycle having 1 to 5 heteroatoms selected from O, N and S; and

R^{10}, R^{30}, R^{70} and R^{100} are defined as:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R}^{150}$;

b) OR^{104} wherein $\mathbf{R}^{104}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R}^{150}$;

c) $OCOR^{105}$ wherein $\mathbf{R}^{105}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R}^{150}$;

d) SR^{108}, $SO_2N(\mathbf{R}^{108})_2$ or $SO_2N(\mathbf{R}^{108})C(O)\mathbf{R}^{108}$ wherein each $\mathbf{R}^{108}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R}^{108}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R}^{150}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R}^{111}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R}^{112}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R}^{115}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both $\mathbf{R}^{111}$ and $\mathbf{R}^{112}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R}^{150}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R}^{116}$ and $\mathbf{R}^{117}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R}^{150}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl,

(C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{150}}$;

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with $\mathbf{R^{150}}$; and

wherein $\mathbf{R^{150}}$ is defined as:

1 to 3 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with $\mathbf{R^{160}}$;

b) OR^{104} wherein $\mathbf{R^{104}}$ is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;.

c) $OCOR^{105}$ wherein $\mathbf{R^{105}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each $\mathbf{R^{108}}$ is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both $\mathbf{R^{108}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

e) $NR^{111}R^{112}$ wherein $\mathbf{R^{111}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and $\mathbf{R^{112}}$ is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein $\mathbf{R^{115}}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both $\mathbf{R^{111}}$ and $\mathbf{R^{112}}$ are

covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

f) $NR^{116}COR^{117}$ wherein $\mathbf{R^{116}}$ and $\mathbf{R^{117}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$;

g) $NR^{118}CONR^{119}R^{120}$, wherein $\mathbf{R^{118}}$, $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{118}}$ is covalently bonded to $\mathbf{R^{119}}$ and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or $\mathbf{R^{119}}$ and $\mathbf{R^{120}}$ are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with $\mathbf{R^{160}}$;

h) $NR^{121}COCOR^{122}$ wherein $\mathbf{R^{121}}$ and $\mathbf{R^{122}}$ is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with $\mathbf{R^{160}}$, or $\mathbf{R^{122}}$ is OR^{123} or $N(R^{124})_2$ wherein $\mathbf{R^{123}}$ and each $\mathbf{R^{124}}$ is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or $\mathbf{R^{124}}$ is OH or O(C_{1-6}alkyl) or both $\mathbf{R^{124}}$ are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with $\mathbf{R^{160}}$;

i) COR^{127} wherein $\mathbf{R^{127}}$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl,

cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with **R**^{160};

j) tetrazole, COOR^{128} wherein **R**^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with **R**^{160}; and

k) CONR^{129}**R**^{130} wherein **R**^{129} and **R**^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both **R**^{129} and **R**^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with **R**^{160};

wherein **R**^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, COOR^{161}, SO_3H, SR^{161}, SO_2**R**^{161}, OR^{161}, N(**R**^{162})$_2$, SO_2N(**R**^{162})$_2$, NR^{162}COR^{162} or CON(**R**^{162})$_2$, wherein **R**^{161} and each **R**^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both **R**^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle,

2. A compound according to claim 1, wherein **R**^{1} is selected from: (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl, or **Het** each of which being optionally substituted with 1 or 2 halogen or from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, each optionally substituted with OR^{11}, SR^{11}, wherein **R**^{11} is independently H, (C_{1-6} alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

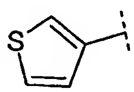
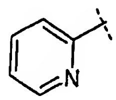
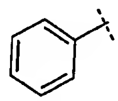
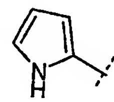
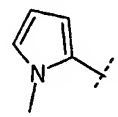
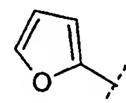
b) OR^{13} wherein **R**^{13} is H, (C_{1-6} alkyl), (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, or **Het**; and

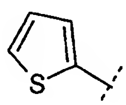
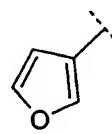
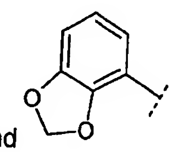
f) a 6- or 10-membered aryl, or **Het** said aryl or **Het** being optionally substituted with (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl.

3. A compound according to claim 2, wherein $\mathbf{R}^1$ is selected from: 6 or 10-membered aryl, or **Het** each of which being optionally substituted with 1 or 2 halogen or with 1 or 2 (C_{1-6})alkyl.

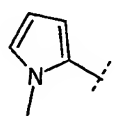
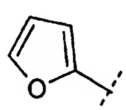
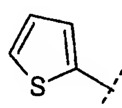
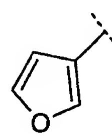
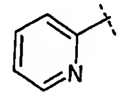
4. A compound according to claim 3, wherein $\mathbf{R}^1$ is phenyl or **Het** optionally substituted with (C_{1-6})alkyl.

5. A compound according to claim 4, wherein $\mathbf{R}^1$ is selected from:

 ;  ;  ;  ;  ;  ;

 ;  ; and  .

6. A compound according to claim 5, wherein $\mathbf{R}^1$ is selected from:

 ;  ;  ;  ; and  .

7. A compound according to claim 1, wherein $\mathbf{R}^2$ is selected from (C_{3-7})cycloalkyl, (C_{6-10})bicycloalkyl, each optionally substituted with 1 or 2 substituents selected from:

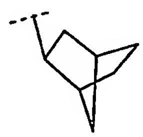
a) halogen, (C_{1-6})alkyl, OH, or (C_{1-6})alkoxy.

8. A compound according to claim 7, wherein $\mathbf{R}^2$ is selected from

(C_{3-7})cycloalkyl, (C_{6-10})bicycloalkyl, each optionally mono- or di-substituted with halogen or (C_{1-6})alkyl.

9. A compound according to claim 8, wherein **R^2** is selected from (C_{3-7})cycloalkyl or (C_{6-10})bicycloalkyl.

10. A compound according to claim 9, wherein **R^2** is cyclopentyl, cyclohexyl, or



11. A compound according to claim 10, wherein **R^2** is cyclopentyl or cyclohexyl.

12. A compound according to claim 1, wherein **B** is N or CR^5, wherein **R^5** is H, halogen, haloalkyl, or (C_{1-6})alkyl.

13. A compound according to claim 12, wherein **B** is N, CH or C-(C_{1-6} alkyl).

14. A compound according to claim 13, wherein **B** is N, CH or C(Me).

15. A compound according to claim 14, wherein **B** is CH.

16. A compound according to claim 1, wherein **X** is N, CH or C-(C_{1-6} alkyl).

17. A compound according to claim 16, wherein **X** is N, CH or C(Me).

18. A compound according to claim 17, wherein **X** is CH.

19. A compound according to claim 1, wherein **D** is CR^5, wherein **R^5** is H, halogen, haloalkyl, or (C_{1-6})alkyl.

20. A compound according to claim 19, wherein **D** is CH or C(Me).

21. A compound according to claim 20, wherein **D** is CH.

22. A compound according to claim 1 wherein $\mathbf{Y^1}$ is O.

23. A compound according to claim 1 wherein $\mathbf{Y^2}$ is O.

24. A compound according to claim 1 wherein both $\mathbf{Y^1}$ and $\mathbf{Y^2}$ are O.

25. A compound according to claim 1, wherein **Z** is N, or NH or O.

26. A compound according to claim 25, wherein **Z** is NH or O.

27. A compound according to claim 26, wherein **Z** is NH.

28. A compound according to claim 1, wherein $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently H, (C_{1-6})alkyl, first (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het** (C_{1-6})alkyl-6- or 10-membered aryl, (C_{1-6})alkyl-**Het**;

or $\mathbf{R^3}$ and $\mathbf{R^4}$ are independently covalently bonded together to form second (C_{3-7})cycloalkyl, 5- or 6-membered heterocycle having from1 to 4 heteroatom selected from O, N, and S;

wherein said alkyl, first and second cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** or heterocycle are optionally substituted with from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{2-4})alkenyl; and

c) $\mathbf{OR^{31}}$ or $\mathbf{COOR^{31}}$, wherein each $\mathbf{R^{31}}$ is independently H or (C_{1-6})alkyl;

or when **Z** is N, either $\mathbf{R^3}$ or $\mathbf{R^4}$ are independently covalently bonded thereto to form a

nitrogen-containing 5-or 6-membered heterocycle.

29. A compound according to claim 28, wherein $\mathbf{R}^3$ and $\mathbf{R}^4$ are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**;

or $\mathbf{R}^3$ and $\mathbf{R}^4$ are covalently bonded together to form cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, 5- or 6-membered heterocycle having from 1 or 2 heteroatom selected from N or S;

wherein said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl or heterocycle are optionally substituted with from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{2-4})alkenyl; and

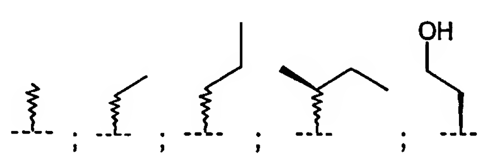
c) OH or $COO(C_{1-6})$alkyl.

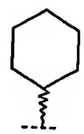
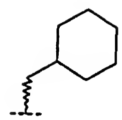
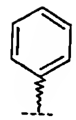
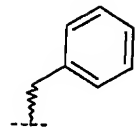
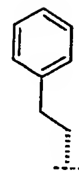
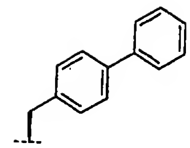
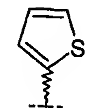
30. A compound according to claim 29, wherein $\mathbf{R}^3$ and $\mathbf{R}^4$ are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6})alkyl-phenyl, (C_{1-6})alkyl-**Het**;

or $\mathbf{R}^3$ and $\mathbf{R}^4$ are covalently bonded together to form cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl all optionally substituted with OH, $(C_{1-6}$ alkyl) or (C_{2-4})alkenyl; or $\mathbf{R}^3$ and $\mathbf{R}^4$ form a piperidine or a pyrrolidine both optionally substituted with $(C_{1-6}$ alkyl) or $COO(C_{1-6})$alkyl.

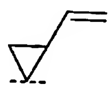
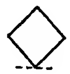
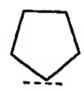
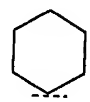
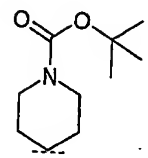
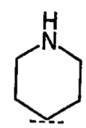
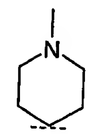
31. A compound according to claim 30, wherein $\mathbf{R}^3$ is H or (C_{1-6})alkyl and $\mathbf{R}^4$ is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-aryl, aryl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or (C_{1-6})alkyl-biaryl.

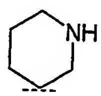
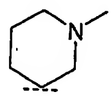
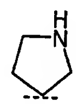
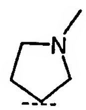
32. A compound according to claim 31, wherein both $\mathbf{R}^3$ and $\mathbf{R}^4$ are H or both CH_3;

or $\mathbf{R}^3$ is H and $\mathbf{R}^4$ is selected from: 

 ;  ;  ;  ;  ;  , and  ; or

$\mathbf{R}^3$ and $\mathbf{R}^4$ are bonded together and form:

 ;  ;  ;  ;  ;;  ;  ;  ;

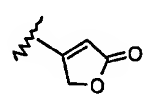
 ;  ,  ; and  .

33. A compound according to claim 1, wherein $\mathbf{R}^7$ is H or (C_{1-6} alkyl).

34. A compound according to claim 33, wherein $\mathbf{R}^7$ is H or Me.

35. A compound according to claim 34, wherein $\mathbf{R}^7$ is H.

36. A compound according to claim 1, wherein **A** is a 6- or 10-membered aryl, **Het** or (C_{1-6}) alkyl-CONH-aryl, said aryl or **Het** being optionally substituted with:

 , halogen, or

- 1 to 2 substituents selected from:
  - a) (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which are optionally substituted with:
    - (C_{1-6})alkyl, (C_{3-7})cycloalkyl; both optionally substituted with a 6 or 10-membered aryl, or **Het**;
    - OR^{101}, $COOR^{101}$ or $CON(R^{101})_2$, wherein each R^{101} is independently H or (C_{1-6})alkyl;

b) OR^{104} wherein R^{104} is H or (C_{1-6}alkyl) optionally substituted with: $COOR^{105}$ or $CON(R^{105})_2$ wherein each R^{105} is independently H or (C_{1-6})alkyl;

d) SR^{108} wherein R^{108} is H or (C_{1-6})alkyl optionally substituted with $COOR^{109}$ or $CON(R^{109})_2$, wherein each R^{109} is independently H or (C_{1-6} alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} and R^{112} are both H; or R^{111} is H and R^{112} is **Het** optionally substituted with (C_{1-6})alkyl or $COOR^{115}$ or $CON(R^{115})_2$, wherein each R^{115} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

j) tetrazole, COOH or COO(C_{1-6})alkyl; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are each independently H or (C_{1-6})alkyl optionally substituted with COOH or COO(C_{1-6})alkyl; and

l) 6- or 10-membered aryl or **Het**, said aryl or **Het** being optionally substituted with from 1 to 4 substituents selected from:

i) (C_{1-6})alkyl or haloalkyl;

ii) OR^{104} wherein R^{104} is H, or (C_{1-6})alkyl) optionally substituted with COOH or COO(C_{1-6})alkyl; and

iii) $COOR^{128}$, $NR^{111}R^{112}$ or $CON(R^{129}R^{130})_2$, wherein R^{128}, R^{111}, R^{112}, R^{129} and R^{130} are independently H or (C_{1-6})alkyl.

37. A compound according to claim 36, wherein **A** is a 6- or 10-membered aryl, or **Het,** said aryl or **Het** being optionally substituted with:

-halogen, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, said alkyl and alkenyl being optionally substituted with:

- OH, (C_{1-6})alkoxy, COOH or $CONH_2$;

b) OH, O(C_{1-6})alkyl)COOH or O(C_{1-6}alkyl)$CONH_2$;

d) SH, S(C_{1-6})alkylCOOH or S(C_{1-6})alkylCONH$_2$;

j) tetrazole, COOH or CONH$_2$; and

l) furan or thiazole mono or di- substituted with:

i) (C_{1-6})alkyl; or

iii) COOH or CONH$_2$.

38. A compound according to claim 37, wherein **A** is phenyl, indole, benzofuran, benzothiophene, coumarin or quinolone, all of which optionally substituted with:

-iodine, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, said alkyl and alkenyl being optionally substituted with:

- OH, (C_{1-6})alkoxy, COOH or CONH$_2$;

b) OH, O(C_{1-6})alkyl)COOH or O(C_{1-6})alkyl)CONH$_2$;

d) SH, S(C_{1-6})alkylCOOH or S(C_{1-6})alkylCONH$_2$;

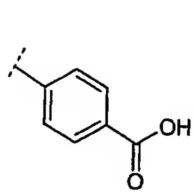
j) COOH or CONH$_2$; and

l) furan or thiazole mono or di- substituted with:

i) (C_{1-6})alkyl; or

iii) COOH or CONH$_2$.

39. A compound according to claim 38, wherein **A** is selected from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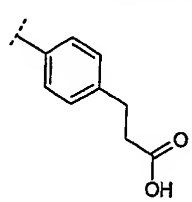
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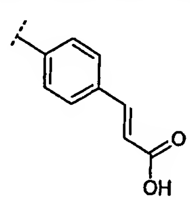
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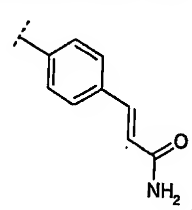
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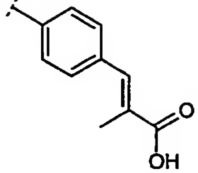
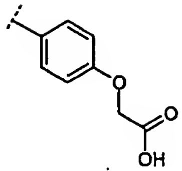
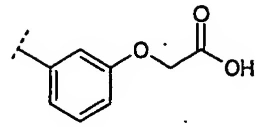
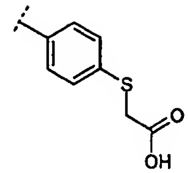
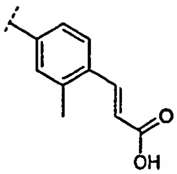
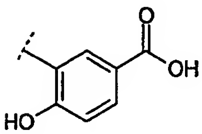
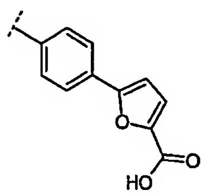
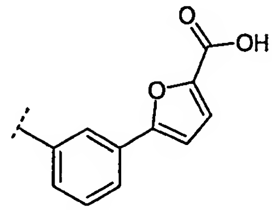
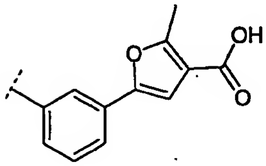
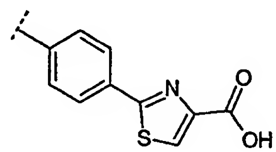
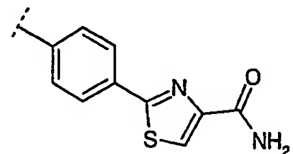
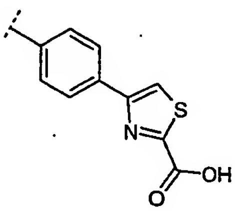
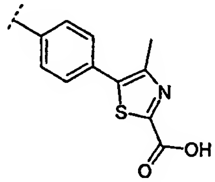
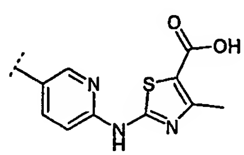
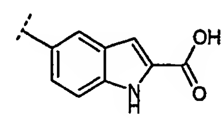
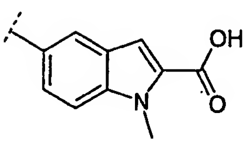
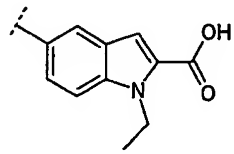
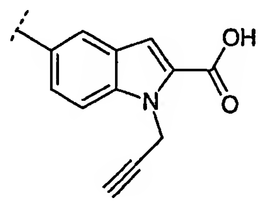
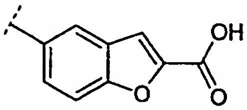
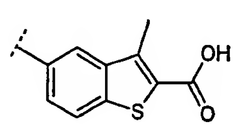
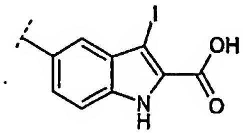
, , , ,

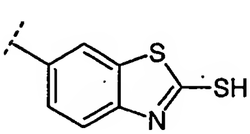
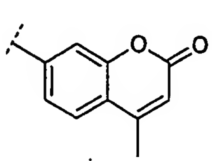
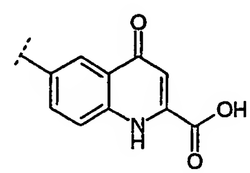
, , , ,

, , ,

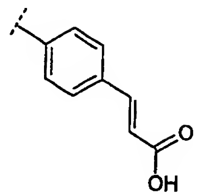
, , , ,

, , ,

, , ,

, , and .

40. A compound according to claim 39, wherein **A** is selected from: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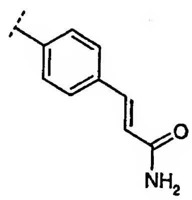
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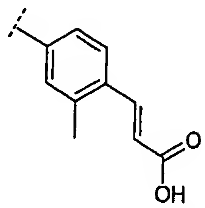
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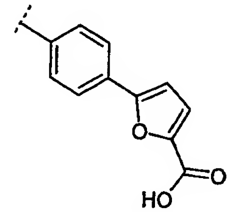
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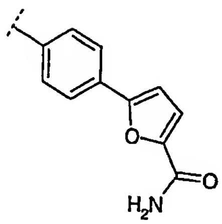
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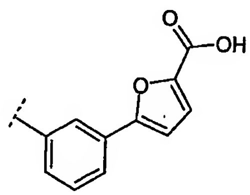
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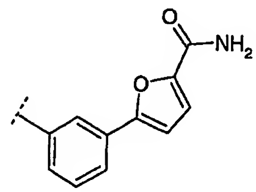
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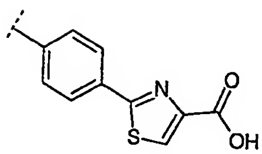
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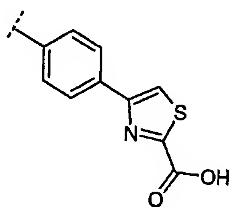
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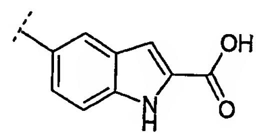
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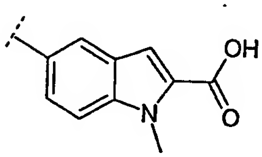
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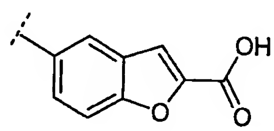
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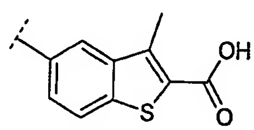
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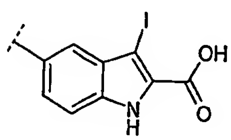
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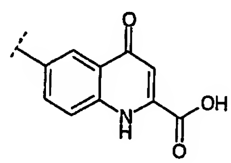
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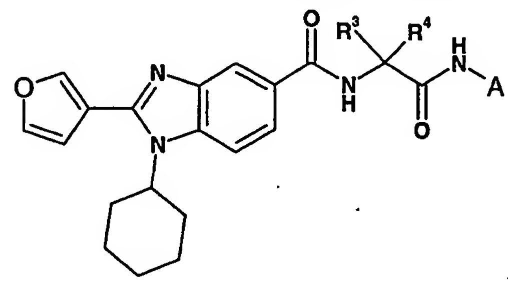
41. A compound according to claim 1, having the following formula:



II

wherein $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently H, (C_{1-6})alkyl, first (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het,** (C_{1-6})alkyl-6- or 10-membered aryl, (C_{1-6})alkyl-**Het**;

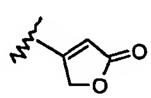
or $\mathbf{R^3}$ and $\mathbf{R^4}$ are independently covalently bonded together to form second (C_{3-7})cycloalkyl, 5- or 6-membered heterocycle having from1 to 4 heteroatom selected from O, N, and S;

wherein said alkyl, first and second cycloalkyl, aryl, **Het,** (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** or heterocycle are optionally substituted with from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{2-4})alkenyl; and

c) OR^{101} or $COOR^{101}$, wherein each $\mathbf{R^{101}}$ is independently H or (C_{1-6})alkyl; and

A is a 6- or 10-membered aryl, **Het** or (C_{1-6}) alkyl-CONH-aryl, said aryl or **Het** being optionally substituted with:



, halogen, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which are optionally substituted with:

- second (C_{1-6})alkyl, second (C_{3-7})cycloalkyl; said second alkyl or second cycloalkyl being optionally substituted with a 6 or 10-membered aryl, or **Het**;

- OR^{101}, $COOR^{101}$ or $CON(R^{101})_2$, wherein each $\mathbf{R^{101}}$ is independently H or (C_{1-6})alkyl;

b) OR^{104} wherein R^{104} is H or (C_{1-6}alkyl) optionally substituted with: COOH, COO(C_{1-6})alkyl or $CONH_2$;

d) SR^{108} wherein R^{108} is H or (C_{1-6})alkyl optionally substituted with COOH, COO(C_{1-6})alkyl or $CONH_2$;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are H; or R^{111} is H and R^{112} is **Het** optionally substituted with (C_{1-6})alkyl, $COOR^{115}$ or $CON(R^{115})_2$, wherein each R^{115} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

j) COOH or COO(C_{1-6})alkyl; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H or (C_{1-6})alkyl optionally substituted with COOH or COO(C_{1-6})alkyl; and

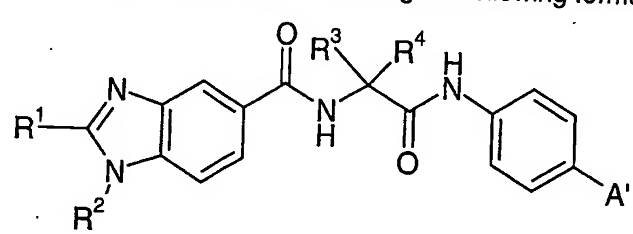
l) 6- or 10-membered aryl or **Het,** said aryl or **Het** being optionally substituted with from 1 to 4 substituents selected from:

i) (C_{1-6})alkyl or haloalkyl;

ii) OR^{104} wherein R^{104} is H, or (C_{1-6})alkyl) optionally substituted with COOH or COO(C_{1-6})alkyl; and

iii) $COOR^{128}$, $NR^{111}R^{112}$ or $CON(R^{129}R^{130})_2$, wherein R^{128}, R^{111}, R^{112}, R^{129} and R^{130} are independently H or (C_{1-6})alkyl.

42. A compound according to claim 1, having the following formula:



III

wherein

R^1 is selected from: (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het,** each of which being optionally substituted with 1 or 2 halogen or from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, each optionally substituted with **OR**[11], **SR**[11], wherein **R**[11] is H, $(C_{1-6}$ alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

b) **OR**[13] wherein **R**[13] is H, $(C_{1-6}$ alkyl), (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, or **Het**; and

f) a 6- or 10-membered aryl or **Het,** said aryl or **Het** being optionally substituted with (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

R^2 is selected from (C_{3-7})cycloalkyl, (C_{6-10})bicycloalkyl, each optionally substituted with 1 or 2 substituents selected from: halogen, (C_{1-6})alkyl, OH, and (C_{1-6})alkoxy;

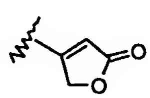
R^3 and **R**^{4} are each independently H, (C_{1-6})alkyl, first (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het** (C_{1-6})alkyl-6- or 10-membered aryl, (C_{1-6})alkyl-**Het**;
or **R**^{3} and **R**^{4} are covalently bonded together to form second (C_{3-7})cycloalkyl, 5- or 6-membered heterocycle having from1 to 4 heteroatom selected from O, N, and S;

wherein said alkyl, first and second cycloalkyl, aryl, **Het,** (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** or heterocycle are optionally substituted with from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{2-4})alkenyl; and

c) **OR**[31] or **COOR**[31], wherein **R**[31] is H or (C_{1-6})alkyl; and

A' is a 6- or 10-membered aryl, **Het** or (C_{1-6}) alkyl-CONH-aryl, said aryl or **Het** being optionally substituted with:


, halogen, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which are optionally substituted with:

- second (C_{1-6})alkyl or second (C_{3-7})cycloalkyl, said second alkyl or second cycloalkyl being optionally substituted with a 6

or 10-membered aryl or **Het**; or

- OR^{101} ,$COOR^{101}$ or $CONH_2$, wherein each R^{101} is independently H or (C_{1-6})alkyl;

b) OR^{104} wherein R^{104} is H or (C_{1-6}alkyl) optionally substituted with: COOH, COO(C_{1-6})alkyl or $CONH_2$;

d) SR^{108} wherein R^{108} is H or (C_{1-6})alkyl optionally substituted with COOH, COO(C_{1-6})alkyl or $CONH_2$;

e) $NR^{111}R^{112}$ wherein R^{111} and R^{112} are both H; or R^{111} is H and R^{112} is **Het** optionally substituted with (C_{1-6})alkyl, $CONH_2$ or $COOR^{115}$ wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

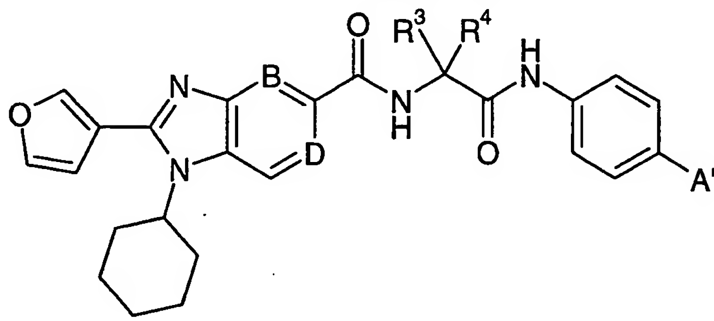
j) COOH or COO(C_{1-6})alkyl;

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are each independently H or (C_{1-6})alkyl optionally substituted with COOH or COO(C_{1-6})alkyl; and

l) 6- or 10-membered aryl or **Het,** said aryl or **Het** being optionally substituted with from 1 to 4 substituents selected from:

- i) (C_{1-6})alkyl or haloalkyl;
- ii) OR^{104} wherein R^{104} is H, or (C_{1-6})alkyl) optionally substituted with COOH or COO(C_{1-6})alkyl; and
- iii) $COOR^{128}$, $NR^{111}R^{112}$ or $CON(R^{129}R^{130})_2$, wherein R^{128}, R^{111}, R^{112}, R^{129} and R^{130} are independently H or (C_{1-6})alkyl.

43. A compound according to claim 1, having the following formula:



IV

wherein

D is CH or C(C_{1-6})alkyl;

B is N, CH, or C(C_{1-6})alkyl;

R^3 and **R**^{4} are each independently H, (C_{1-6})alkyl, first (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-6- or 10-membered aryl, (C_{1-6})alkyl-**Het**;

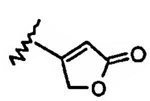
or **R**^{3} and **R**^{4} are covalently bonded together to form second (C_{3-7})cycloalkyl, 5- or 6-membered heterocycle having from1 to 4 heteroatom selected from O, N, and S;

wherein said alkyl, first and second cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** or heterocycle are optionally substituted with from 1 or 2 substituents selected from:

a) (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{2-4})alkenyl; and

c) **OR**^{31} or **COOR**^{31}, wherein **R**^{31} is H or (C_{1-6})alkyl; and

A' is a 6- or 10-membered aryl, **Het** or (C_{1-6}) alkyl-CONH-aryl, said aryl or **Het** being optionally substituted with:



, halogen, or

- 1 to 2 substituents selected from:

a) (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, all of which are optionally substituted with:

- second (C_{1-6})alkyl or second (C_{3-7})cycloalkyl, said second alkyl or second cycloalkyl being optionally substituted with a 6 or 10-membered aryl or **Het**;

- OR^{101}, $COOR^{101}$ or $CONH_2$, wherein each R^{101} is independently H or (C_{1-6})alkyl;

b) OR^{104} wherein R^{104} is H or (C_{1-6}alkyl) optionally substituted with: COOH, $COO(C_{1-6})$alkyl or $CONH_2$;

d) SR^{108} wherein R^{108} is H or (C_{1-6})alkyl optionally substituted with COOH, $COO(C_{1-6})$alkyl or $CONH_2$;

e) $NR^{111}R^{112}$ wherein R^{111} and R^{112} are both H; or R^{111} is H and R^{112} is **Het** optionally substituted with (C_{1-6})alkyl, $CONH_2$ or $COOR^{115}$ wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl;

j) COOH or $COO(C_{1-6})$alkyl;

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are each independently H or (C_{1-6})alkyl optionally substituted with COOH or $COO(C_{1-6})$alkyl; and

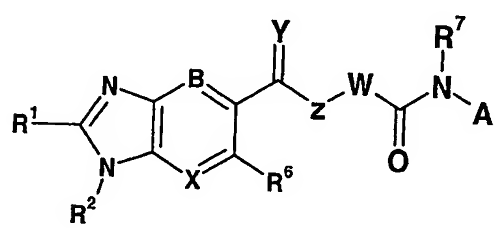
l) 6- or 10-membered aryl or **Het,** said aryl or **Het** being optionally substituted with from 1 to 4 substituents selected from:

i) (C_{1-6})alkyl or haloalkyl;

ii) OR^{104} wherein R^{104} is H, or (C_{1-6})alkyl) optionally substituted with COOH or $COO(C_{1-6})$alkyl; and

iii) $COOR^{128}$, $NR^{111}R^{112}$ or $CON(R^{129}R^{130})_2$, wherein R^{128}, R^{111}, R^{112}, R^{129} and R^{130} are independently H or (C_{1-6})alkyl.

44. A compound of formula Ia:



Ia

wherein R^1 is selected from: 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S and phenyl, said heterocycle and phenyl being optionally substituted with from 1 to 4 (C_{1-4})alkyl substituents;

R^2 is selected from: (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-3})alkyl, and norbornane;

X is CH or N;
R^6 is H or (C_{1-6} alkyl);
Y is O or S;
B is N or CR^5, wherein R^5 is H or (C_{1-6}) alkyl with the proviso that **X** and **B** are not both N;
Z is O, N, or NH;
W is CR^3R^4 wherein R^3 and R^4 are each independently H, (C_{1-6} alkyl), (C_{3-7} cycloalkyl), (C_{1-6} alkyl)phenyl, (C_{1-6} alkyl)-(C_{3-7} cycloalkyl), (C_{3-7} cycloalkyl)-(C_{1-6} alkyl), (C_{3-7} cycloalkyl)-(C_{2-4} alkenyl), (C_{1-6} alkyl)-OH, phenyl, CH_2biphenyl, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S, (C_{1-6} alkyl)-5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, or (C_{1-6} alkyl)-9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S, or R^3 and R^4 are covalently bonded together to form (C_{3-7} cycloalkyl), 4-, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S; or when **Z** is N, either R^3 or R^4 is covalently bonded thereto to form a 5-membered heterocycle;

> wherein said alkyl, cycloalkyl, heterocycle, heterobicycle, phenyl are optionally substituted with from 1 to 4 substituents selected from: OH, COOH, (C_{1-6} alkyl), (C_{2-4} alkenyl), $CONH_2$, NH_2, NH(C_{1-6} alkyl), N(C_{1-6} alkyl)$_2$, NHCOCOOH, NHCOCON(C_{1-6} alkyl)$_2$, NHCOCONH(C_{1-6} alkyl), SH, S(C_{1-6} alkyl), NHC(=NH)NH_2, and COO(C_{1-6}alkyl);

R^7 is H or (C_{1-6} alkyl);

A is selected from: (C_{1-3}alkyl)CONHaryl, 6- or 10-membered aryl, biphenyl, 5- or 6-atom heterocycle having 1 to 4 heteroatoms selected from O, N and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

wherein said aryl, biphenyl, first heterocycle, and heterobicycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, COO(C_{1-6})alkyl, (C_{1-6})alkyl, (C_{1-6})alkylCOOH, (C_{1-6} alkyl)(C_{2-4} alkynyl), (C_{1-6})alkyl-hydroxy, phenyl, benzyloxy, halogen, (C_{2-4})alkenyl, (C_{2-4})alkenyl-(C_{1-6})alkyl-COOH, 5- or 6-membered second heterocycle having 1 to 4 heteroatoms selected from O, N and S, NH-5- or 6- membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S,

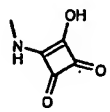
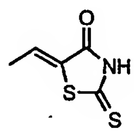
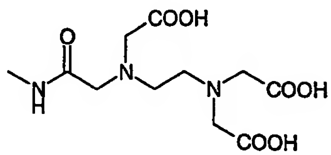
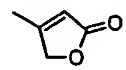
wherein said second heterocycle and phenyl being optionally substituted with from 1 to 4 substituents selected from: (C_{1-6} alkyl), CF_3, OH, (C_{1-6}alkyl) COOH, O(C_{1-6}alkyl)COOH, (C_{1-6}alkyl) COO(C_{1-6}alkyl), CH_2phenyl, COO(C_{1-6} alkyl), (C_{1-6}alkyl)O(C_{1-6}alkyl), COOH, NCH(C_{1-6}alkyl)$_2$, NCO(C_{1-6} alkyl), NH_2, NH(C_{1-6} alkyl), and N(C_{1-6} alkyl)$_2$;

halogen, OPO_3H, benzyl, sulfonamido, SH, $SOCH_3$, SO_3H, SO_2CH_3, S(C_{1-6} alkyl)COOH, $-CONH_2$, $-COCH_3$, (C_{1-3})alkyl, (C_{2-4}alkenyl)COOH

wherein said alkenyl is optionally substituted with from 1 to 2 (C_{1-6} alkyl) substituents,

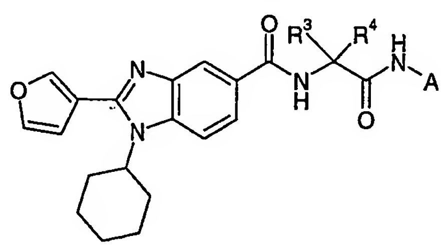
(C_{2-4}alkenyl)COO(C_{1-6}alkyl), tetrazolyl, COOH, triazolyl, OH, NO_2, NH_2, $-O(CH_2)_p$COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-6} alkyl)COOH, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, -NHCOCOOH, -NHCOCONHOH,-NHCOCONH$_2$, -NHCOCONHCH$_3$, -NHCO(C_{1-6})alkyl-COOH, -NHCOCONH(C_{1-6})alkyl-COOH, -NHCO(C_{3-7})cycloalkyl-COOH, -NHCONH(C_{6-10})aryl-COOH, - NHCONH(C_{6-10})aryl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-COOH,- NHCONH(C_{1-6})alkyl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-(C_{2-6})alkenyl-COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-O(C_{1-6})alkyl COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-COOH, -NHCH$_2$COOH,

-$NHCONH_2$, -NHCO(C_{1-6})hydroxyalkyl COOH, -OCO(C_{1-6})hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,

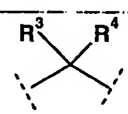
, , , , -NHCN, -NHCHO, -$NHSO_2CH_3$, -$NHSO_2CF_3$, coumarin, (C_{1-6})alkyl-amino, di-(C_{1-6})alkyl-amino, C(halogen)$_3$, -NH(C_{2-4})acyl, -NH(C_{6-10})aroyl, -CONH(C_{1-6}alkyl), -CO(C_{1-6})alkyl-COOH, -CONH(C_{1-6})alkyl-COOH, -CO-NH-alanyl, -CONH(C_{2-4})alkylN(C_{1-6}alkyl)$_2$, -CONH(C_{2-4}) alkyl-**Het** -CONH(C_{2-4}) alkyl-(COOH)-**Het**-CONH(C_{1-2} alkyl) (OH)(C_{1-2} alkyl) OH, -CONH(C_{1-6}) alkyl-COOH, -CONH(C_{6-10} aryl), -CONH-**Het** -CONH(C_{6-10}) aryl-COOH, -CONH(C_{6-10}) aryl-COO(C_{1-6}) alkyl, -CONH(C_{1-6}) alkyl-COO(C_{1-6}) alkyl, -CONH(C_{6-10}) aryl-(C_{1-6})alkyl-COOH, -CONH(C_{6-10}) aryl-(C_{2-6})alkenyl-COOH;

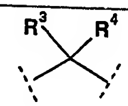
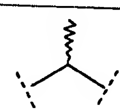
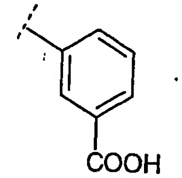
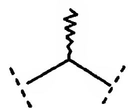
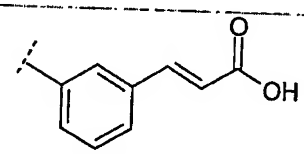
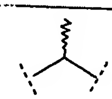
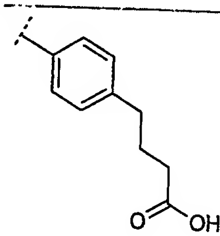
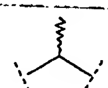
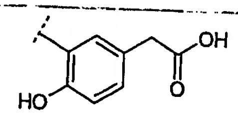
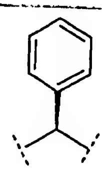
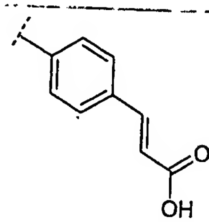
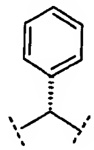
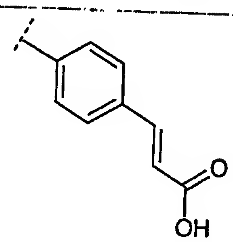
or salt thereof.

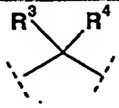
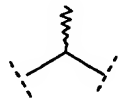
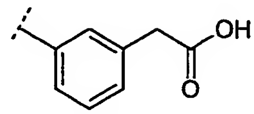
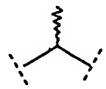
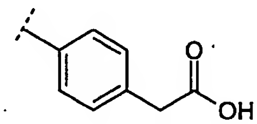
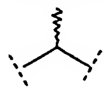
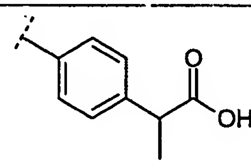
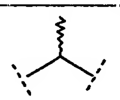
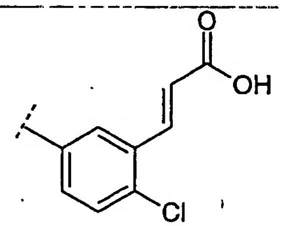
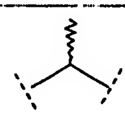
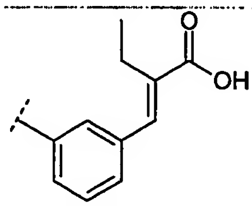
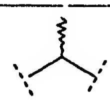
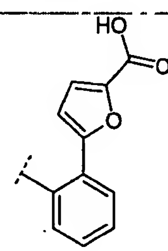
45. A compound according to claim 1 having the following formula:

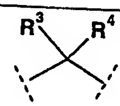
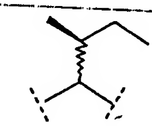
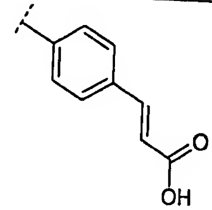
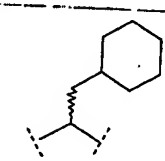
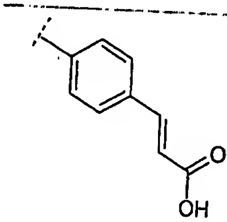
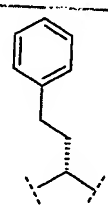
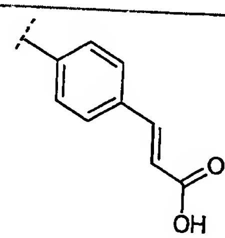
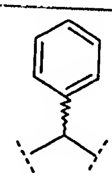
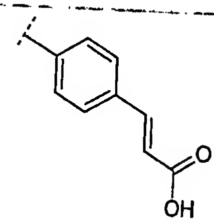
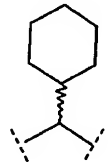
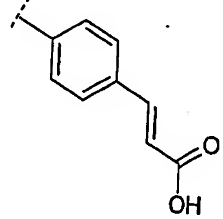


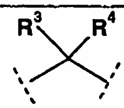
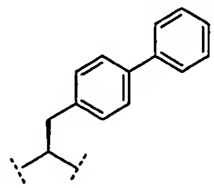
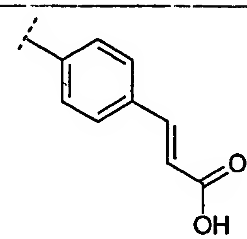
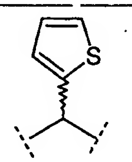
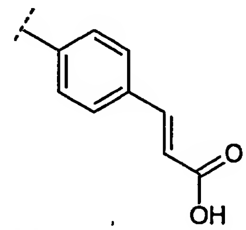
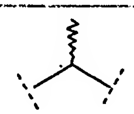
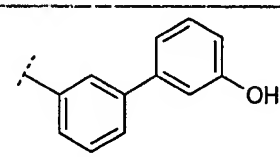
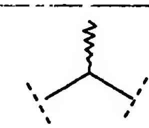
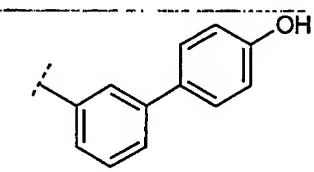
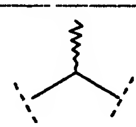
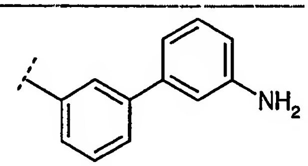
wherein **R^3**, **R^4** and **A** are as defined below:

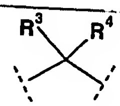
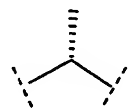
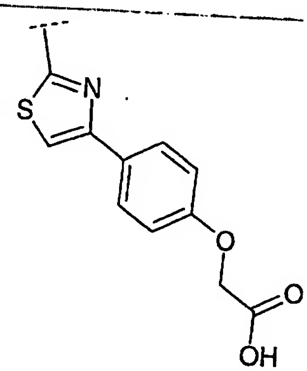
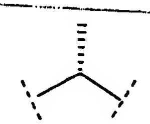
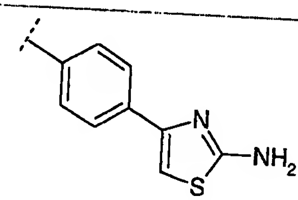
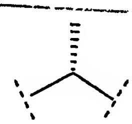
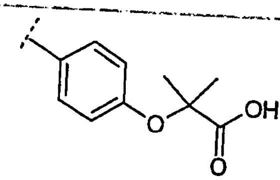
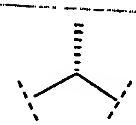
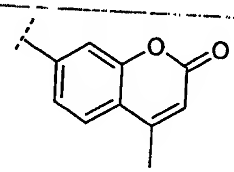
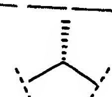
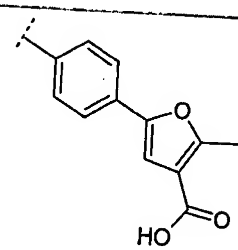
Cmpd. #		**A**

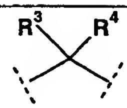
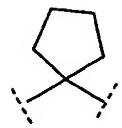
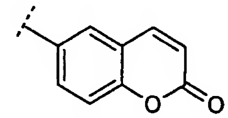
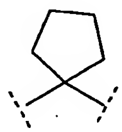
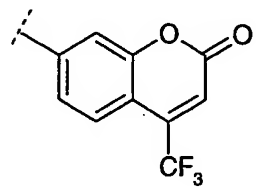
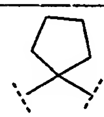
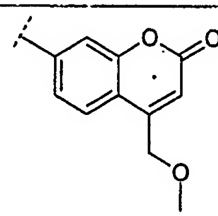
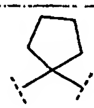
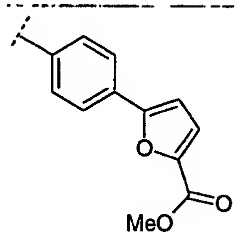
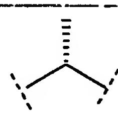
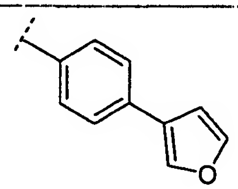
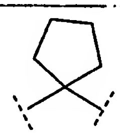
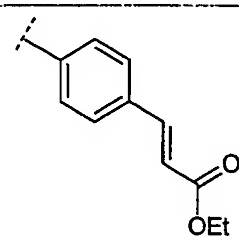
Cmpd. #		A
1001		 ;
1002		 ;
1003		 ;
1004		 ;
1005		 ;
1006		 ;

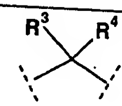
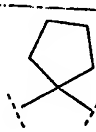
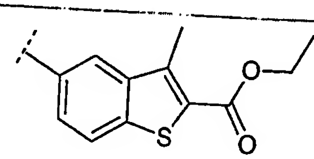
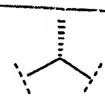
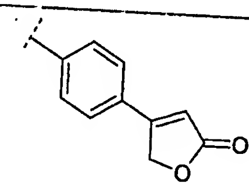
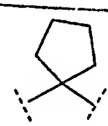
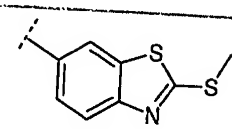
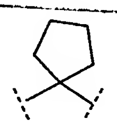
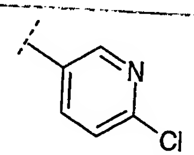
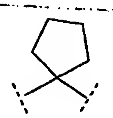
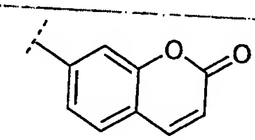
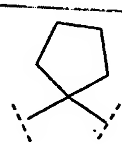
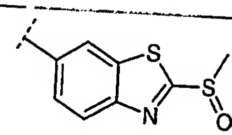
Cmpd. #		A	
1007			;
1008			;
1009			;
1010			;
1011			;
1012			;

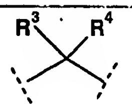
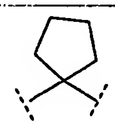
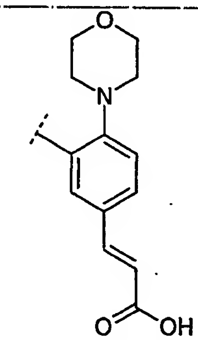
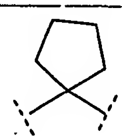
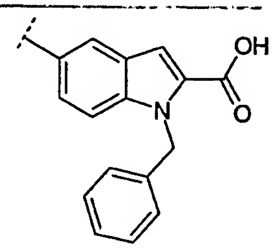
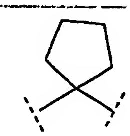
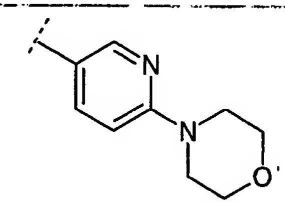
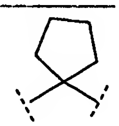
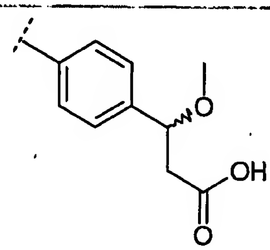
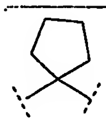
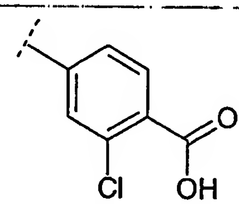
Cmpd. #		A
1013		 ;
1014		 ;
1015		 ;
1016		 ;
1017		 ;

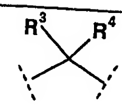
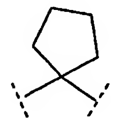
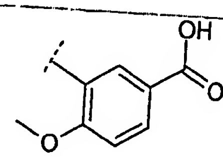
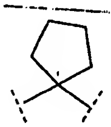
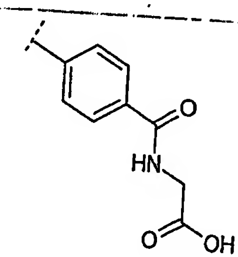
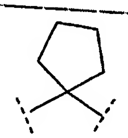
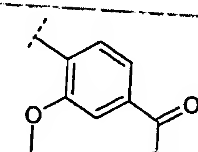
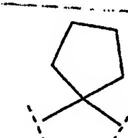
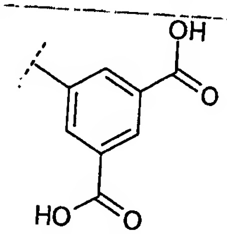
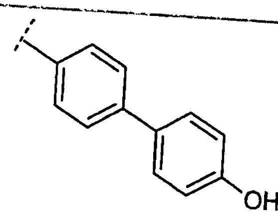
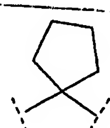
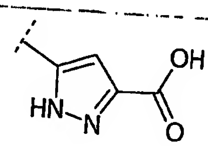
Cmpd. #		A
1018		 ;
1019		 ;
1020		 ;
1021		 ;
1022		 ;

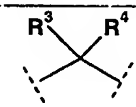
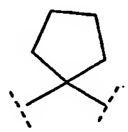
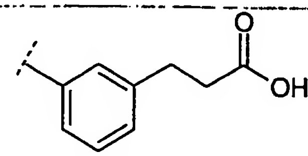
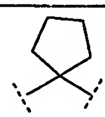
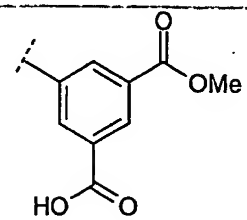
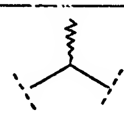
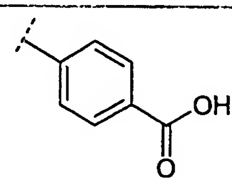
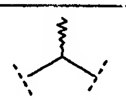
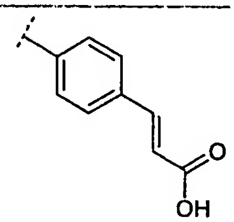
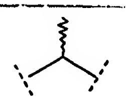
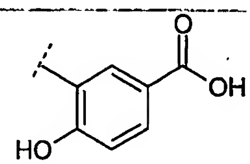
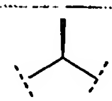
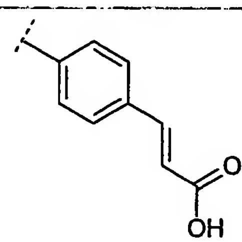
Cmpd. #		A
1023		 ;
1024		 ;
1025		 ;
1026		 ;
1027		 ;

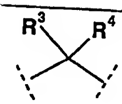
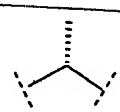
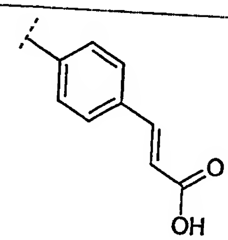
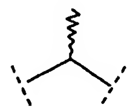
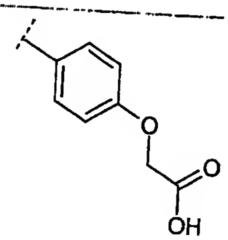
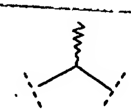
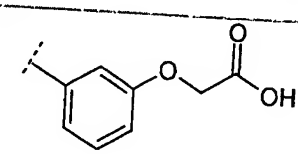
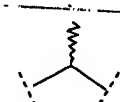
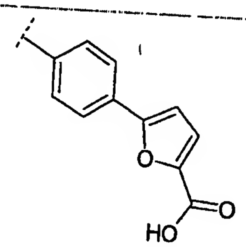
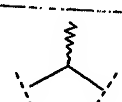
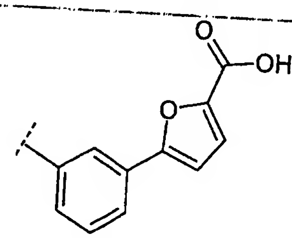
Cmpd. #		A	
1028			;
1029			;
1030			;
1031			;
1032			;
1033			;

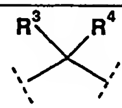
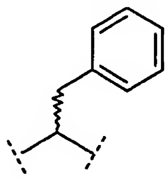
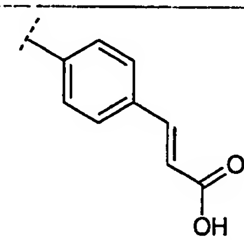
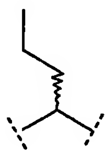
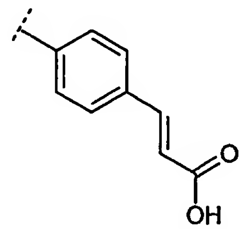
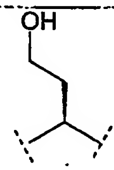
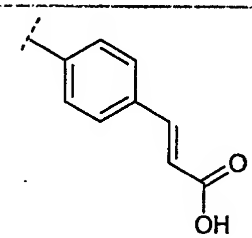
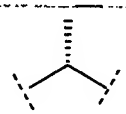
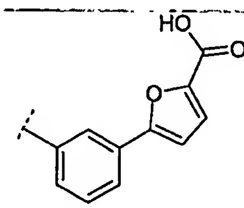
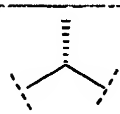
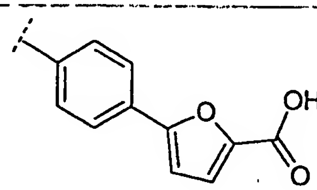
Cmpd. #		A
1034		 ;
1035		 ;
1036		 ;
1037		 ;
1038		 ;
1039		 ;

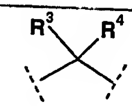
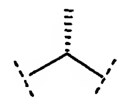
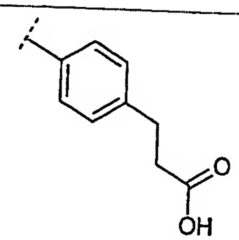
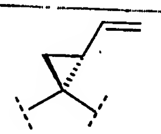
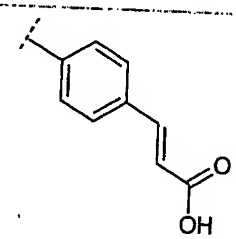
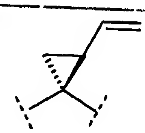
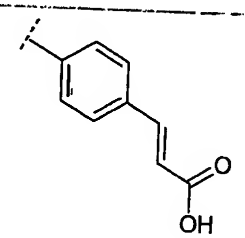
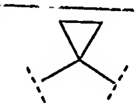
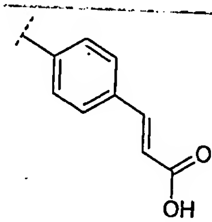
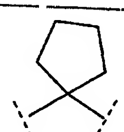
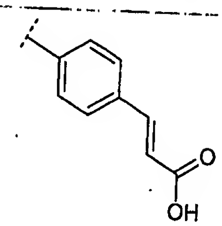
Cmpd. #		A
1040		 ;
1041		 ;
1042		 ;
1043		 ;
1044		 ;

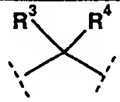
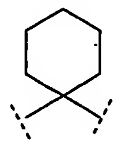
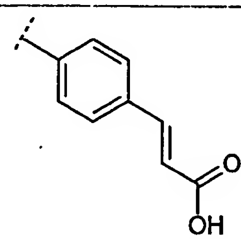
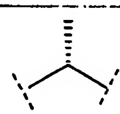
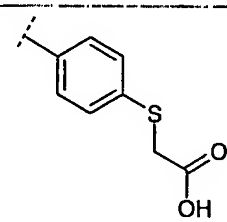
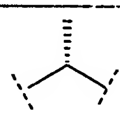
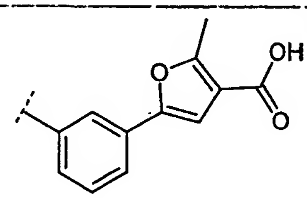
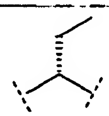
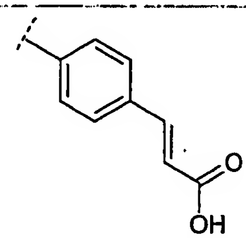
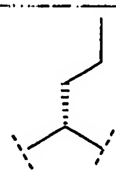
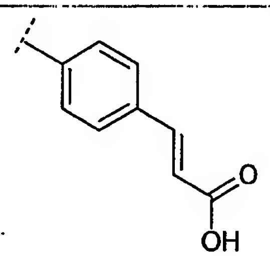
Cmpd. #		A
1045		 ;
1046		 ;
1047		 ;
1048		 ;
1049		 ;
1050		 ;

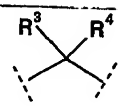
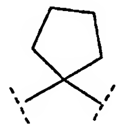
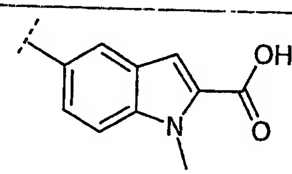
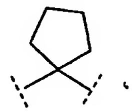
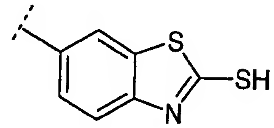
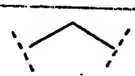
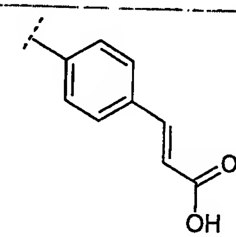
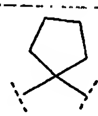
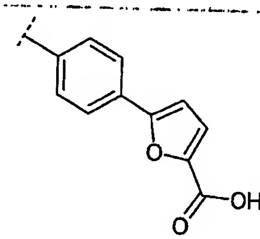
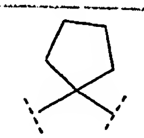
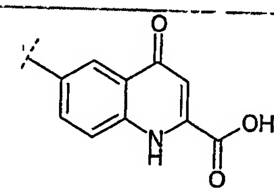
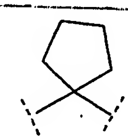
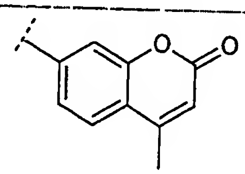
Cmpd. #		A	
1051			;
1052			;
1053			;
1054			;
1055			;
1056			;

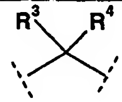
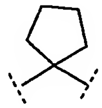
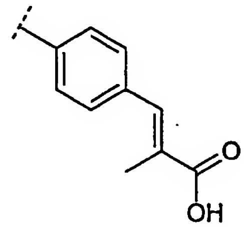
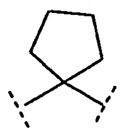
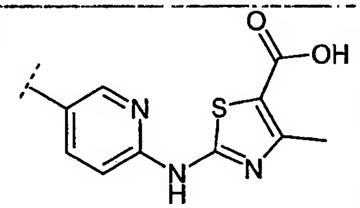
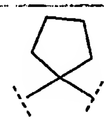
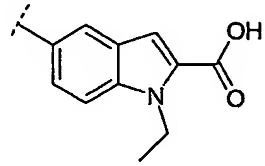
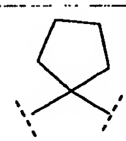
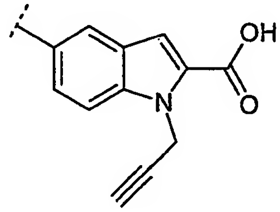
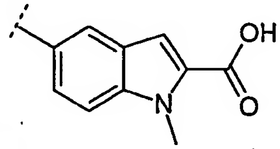
Cmpd. #		A
1057		 ;
1058		 ;
1059		 ;
1060		 ;
1061		 ;

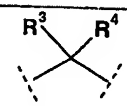
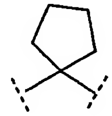
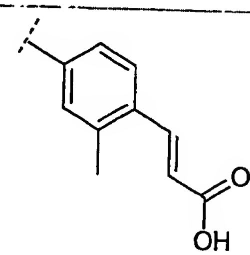
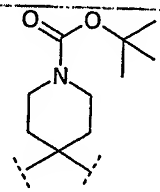
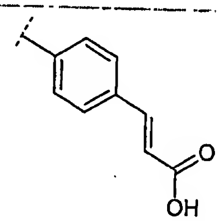
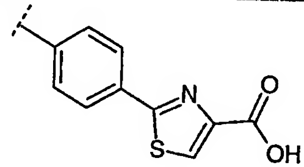
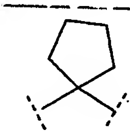
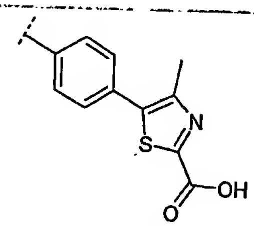
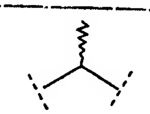
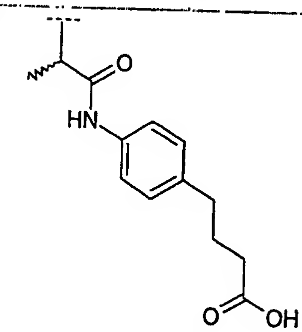
Cmpd. #		A
1062		 ;
1063		 ;
1064		 ;
1065		 ;
1066		 ;

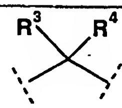
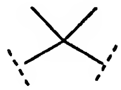
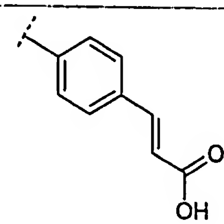
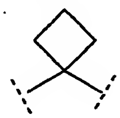
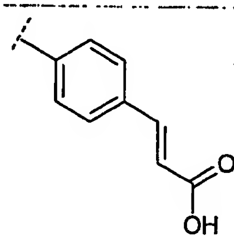
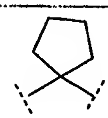
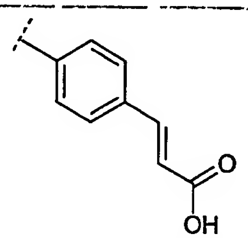
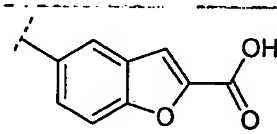
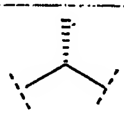
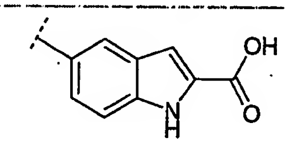
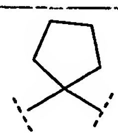
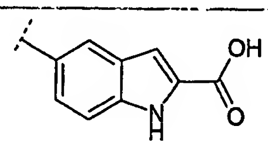
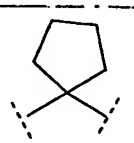
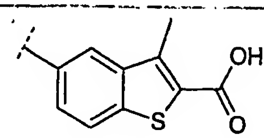
Cmpd. #		A
1067		 ;
1068		 ;
1069		 ;
1070		 ;
1071		 ;

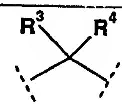
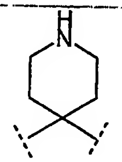
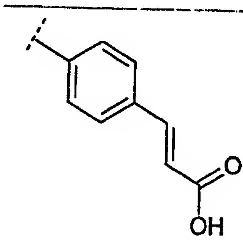
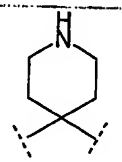
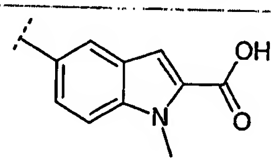
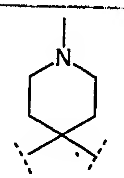
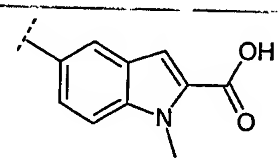
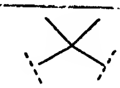
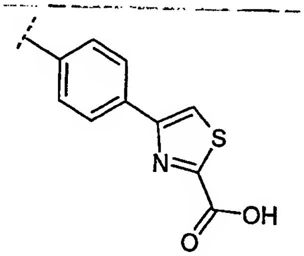
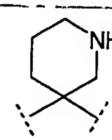
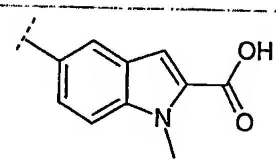
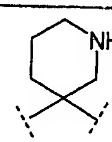
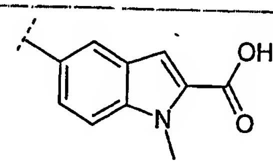
Cmpd. #		A
1072		 ;
1073		 ;
1074		 ;
1075		 ;
1076		 ;

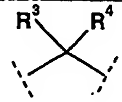
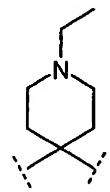
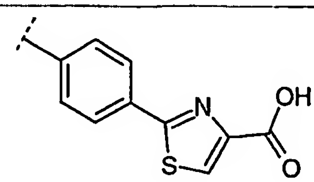
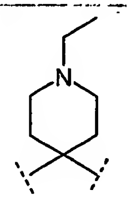
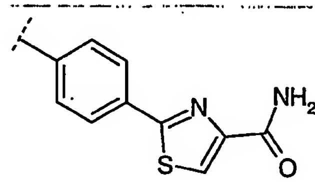
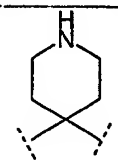
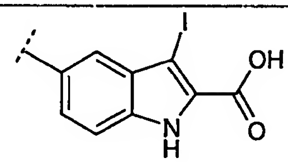
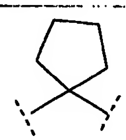
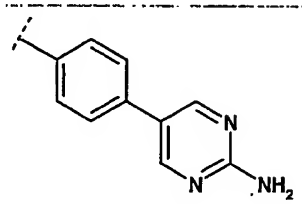
Cmpd. #		A
1077		 ;
1078		 ;
1079		 ;
1080		 ;
1081		 ;
1082		 ;

Cmpd. #		A
1083		 ;
1084		 ;
1085		 ;
1086		 ;
1087		 ;

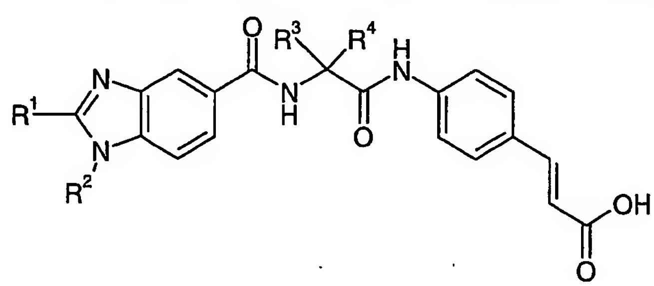
Cmpd. #		A
1088		 ;
1089		 ;
1090		 ;
1091		 ;
1092		 ;

Cmpd. #		A
1093		 ;
1094		 ;
1095		 ;
1096		 ;
1097		 ;
1098		 ;
1099		 ;

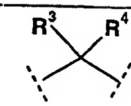
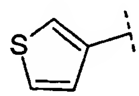
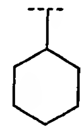
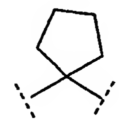
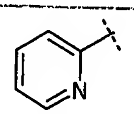
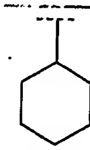
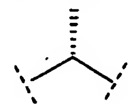
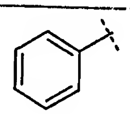
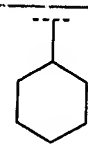
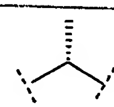
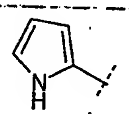
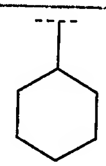
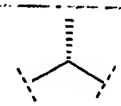
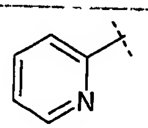
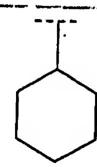
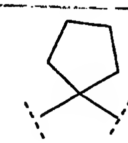
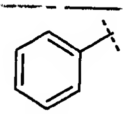
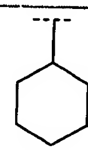
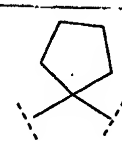
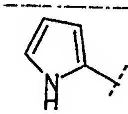
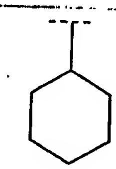
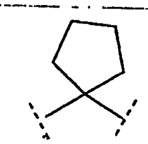
Cmpd. #		A	
1100			;
1101			;
1102			;
1103			;
1104	 (+) enantiomer		;
1105	 (-) enantiomer		;

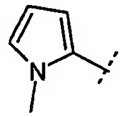
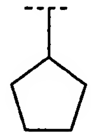
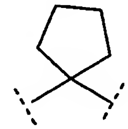
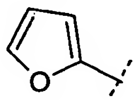
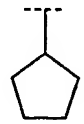
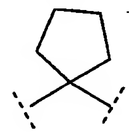
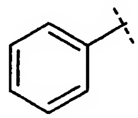
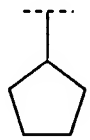
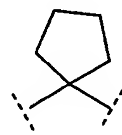
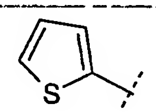
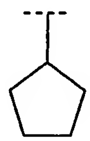
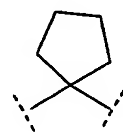
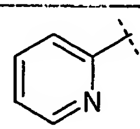
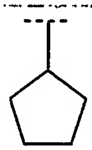
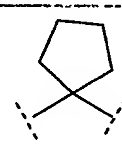
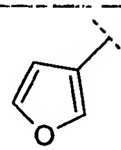
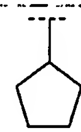
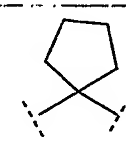
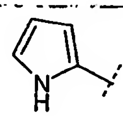
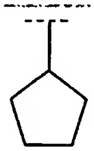
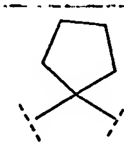
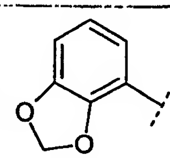
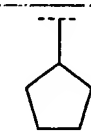
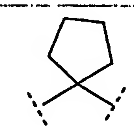
Cmpd. #		A
1108		 ;
1109		 ;
1110		 ; and
1111		 .

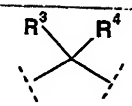
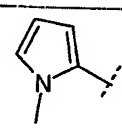
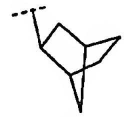
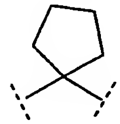
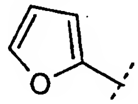
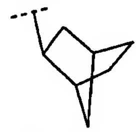
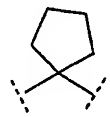
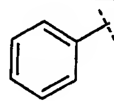
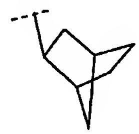
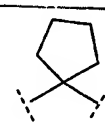
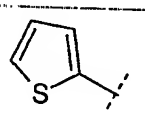
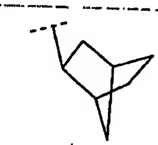
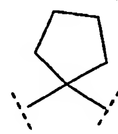
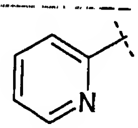
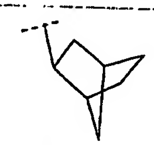
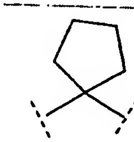
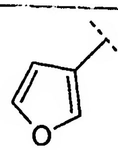
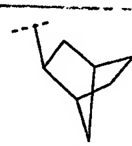
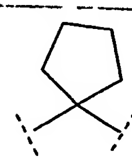
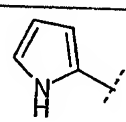
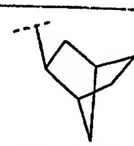
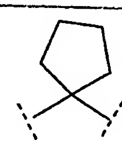
46. A compound according to claim 1 having the following formula:

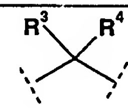
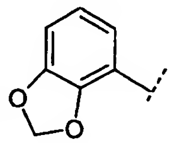
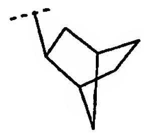
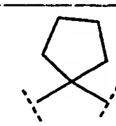
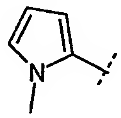
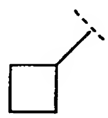
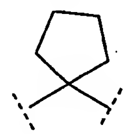
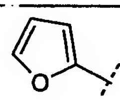
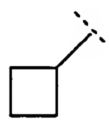
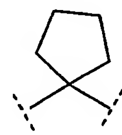
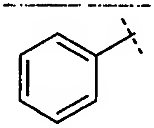
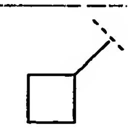
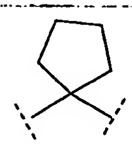
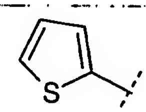
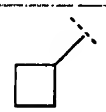
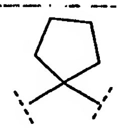
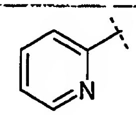
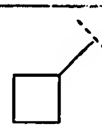
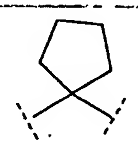
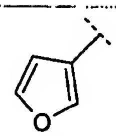
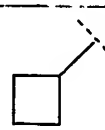
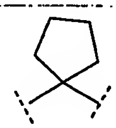
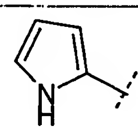
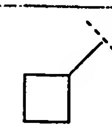
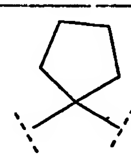


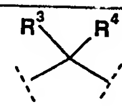
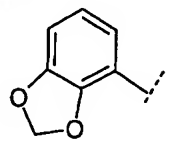
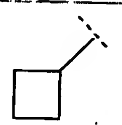
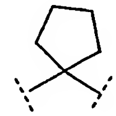
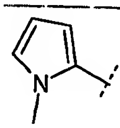
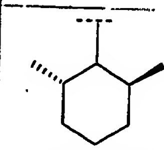
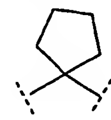
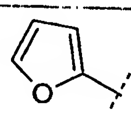
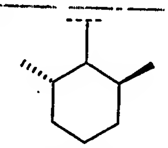
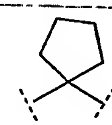
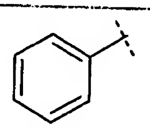
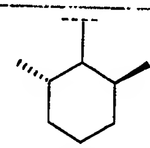
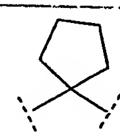
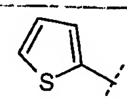
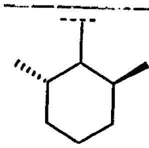
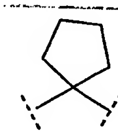
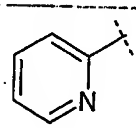
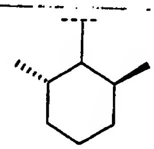
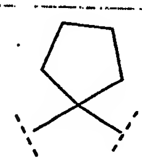
wherein **R^1**, **R^2**, **R^3**, and **R^4** are as defined below:

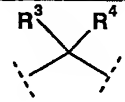
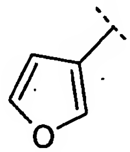
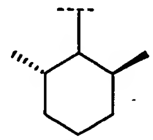
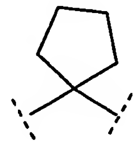
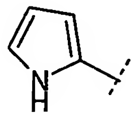
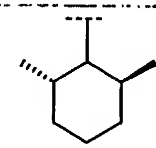
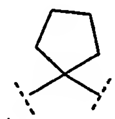
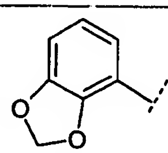
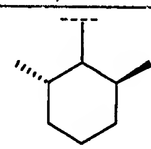
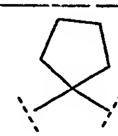
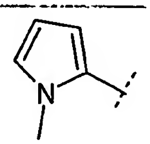
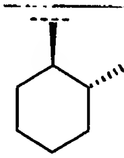
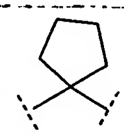
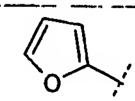
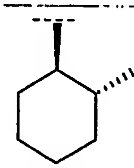
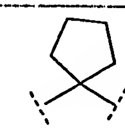
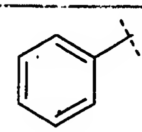
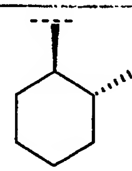
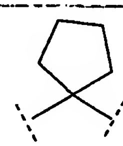
Cmpd. #	R¹	R²	
2001			 ;
2002			 ;
2003			 ;
2004			 ;
2005			 ;
2006			 ;
2007			 ;

Cmpd. #	R^1	R^2	R^3 R^4 	
2008				;
2009				;
2010				;
2011				;
2012				;
2013				;
2014				;
2015				;

Cmpd. #	R^1	R^2	
2016		 Racemic mixture	 ;
2017		 Racemic mixture	 ;
2018		 Racemic mixture	 ;
2019		 Racemic mixture	 ;
2020		 Racemic mixture	 ;
2021		 Racemic mixture	 ;
2022		 Racemic mixture	 ;

Cmpd. #	R^1	R^2		
2023		 Racemic mixture		;
2024				;
2025				;
2026				;
2027				;
2028				;
2029				;
2030				;

Cmpd. #	R^1	R^2	
2031			 ;
2032		 Mixture of enantiomers/ diastereoisomers	 ;
2033		 Mixture of enantiomers/ diastereoisomers	 ;
2034		 Mixture of enantiomers/ diastereoisomers	 ;
2035		 Mixture of enantiomers/ diastereoisomers	 ;
2036		 Mixture of enantiomers/ diastereoisomers	 ;

Cmpd. #	R^1	R^2		
2037		 Mixture of enantiomers/ diastereoisomers		;
2038		 Mixture of enantiomers/ diastereoisomers		;
2039		 Mixture of enantiomers/ diastereoisomers		;
2040		 Racemic mixture		;
2041		 Racemic mixture		;
2042		 Racemic mixture		;

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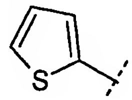
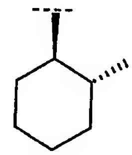
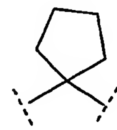
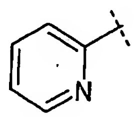
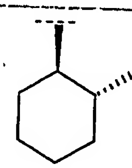
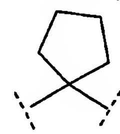
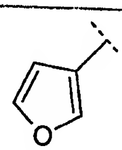
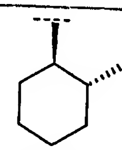
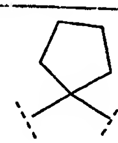
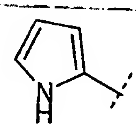
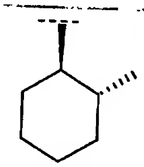
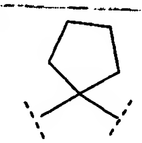
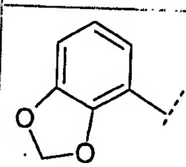
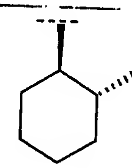
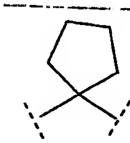
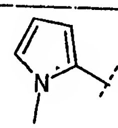
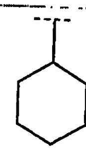
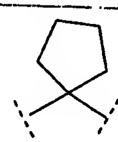
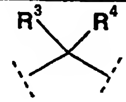
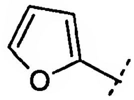
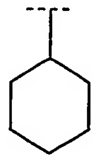
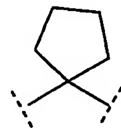
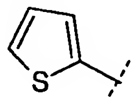
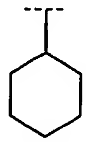
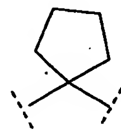
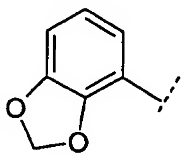
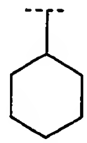
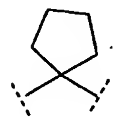
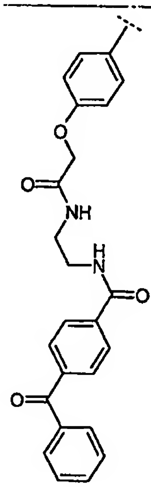
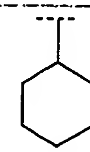
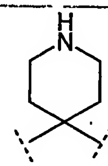
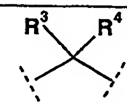
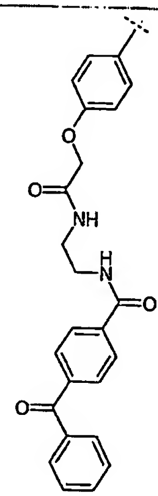
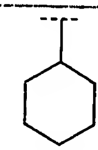
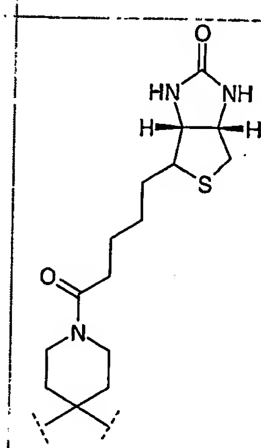
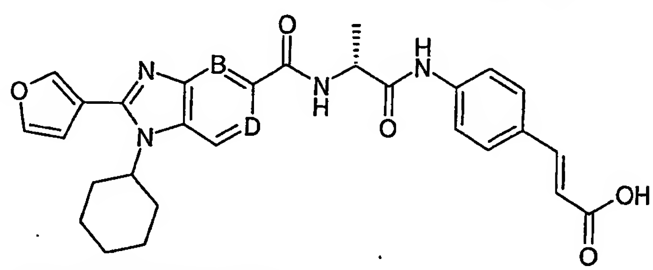
2043		 Racemic mixture	 ;
2044		 Racemic mixture	 ;
2045		 Racemic mixture	 ;
2046		 Racemic mixture	 ;
2047		 Racemic mixture	 ;
2048			 ;

Cmpd. #	R^1	R^2		
2049				;
2050				;
2051				;
2052				; and

Cmpd. #	R^1	R^2	
2053			

47. A compound according to claim 1 having the following formula:



wherein **B** and **D** are as defined below:

Compound entry #	B	D
3001	N	CH
3002	CH	CMe
3003	CMe	CH

; ; and .

48. A pharmaceutical composition for the treatment or prevention of HCV infection, comprising an effective amount of a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically

acceptable carrier.

49. A composition according to claim 48, further comprising an immunomodulatory agent.

50. A composition according to claim 49, wherein said immunomodulatory agents is selected from: α-, β-, δ- γ-, and ω-interferon.

51. A composition according to claim 48, further comprising another antiviral agent.

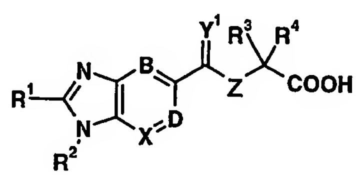
52. A composition according to claim 51, wherein said antiviral agent is selected from: ribavirin and amantadine.

53. A composition according to claim 48, further comprising another inhibitor of HCV polymerase.

54. A composition according to claim 48, further comprising an inhibitor of HCV selected from: HCV helicase, HCV protease, HCV metalloprotease or HCV IRES.

55. Use of a compound of formula I according to claim 1, for the manufacture of a medicament for the treatment of HCV infection.

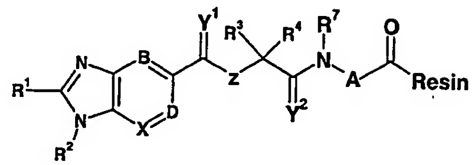
56. An intermediate compound of formula (i):



(i)

wherein **R^1**, **R^2**, **R^3**, **R^4**, **B**, **D**, **X**, **Y^1**, and **Z** are as defined in claim 1, or a derivative thereof.

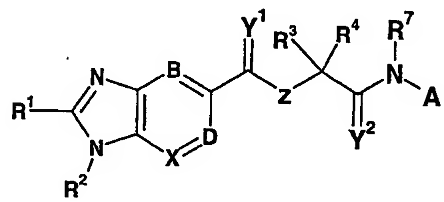
57. An intermediate compound of formula I(ii):



I(ii)

wherein **R^1**, **R^2**, **R^3**, **R^4**, **R^7**, **A**, **B**, **D**, **X**, **Y^1**, **Y^2** and **Z** are as defined in claim 1, or a derivative thereof.

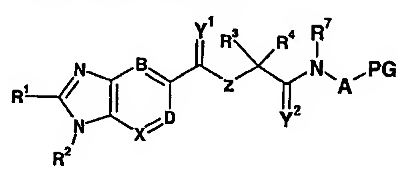
58. A process for producing compounds of formula I,



I

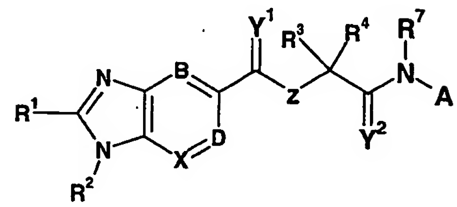
wherein **R^1**, **R^2**, **R^3**, **R^4**, **R^7**, **A**, **B**, **D**, **X**, **Y^1**, **Y^2** and **Z** are as defined in claim 1, comprising:

a) removing, in a mixture of an aqueous base or an aqueous acid in a co-solvent, the protecting group (PG) from:



wherein **R^1**, **R^2**, **R^3**, **R^4**, **R^7**, **A**, **B**, **D**, **X**, **Y^1**, **Y^2** and **Z** are as defined in claim 1, and wherein **PG** is a carboxylic acid protecting group, so as to produce compounds of formula I.

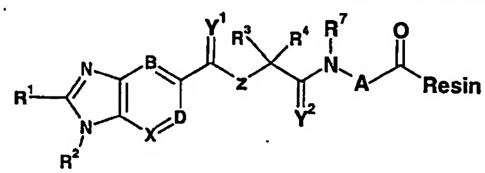
59. A process for producing compounds of formula I,



I

wherein **R^1**, **R^2**, **R^3**, **R^4**, **R^7**, **A**, **B**, **D**, **X**, **Y^1**, **Y^2** and **Z** are as defined in claim 1, comprising:

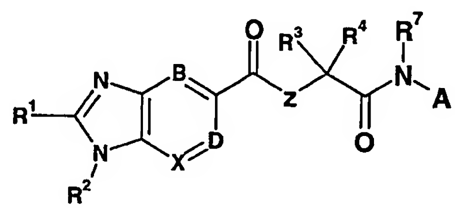
a) cleaving, under acidic conditions, intermediate compound I(ii)



I(ii) ,

so as to produce compounds of formula I, where **R^1**, **R^2**, **R^3**, **R^4**, **R^7**, **A**, **B**, **D**, **X**, **Y^1** and **Y^2** are as defined in claim 1.

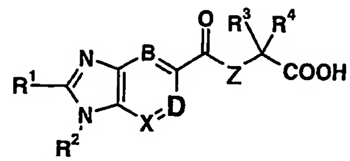
60. A process for producing compounds of formula I,



I

wherein **R^1**, **R^2**, **R^3**, **R^4**, **R^7**, **A**, **B**, **D**, **X**, and **Z** are as defined in claim 1, comprising:

i) coupling intermediate compound of formula (i):



(i)

wherein R^1, R^2, R^3, R^4, **B**, **D**, **X**, and **Z** are as defined in claim 1, or a derivative thereof,

with HN(**R^7**)-**A** wherein **R^7** and **A** are as defined in claim 1, to produce a compound of formula I.

SEQUENCE LISTING

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<150> 60/338,324
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        35                  40                  45
Ser Gln Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Val Arg His Arg
    50                  55                  60
Asn Met Val Tyr Ser Thr Thr Ser Arg Ser Ala Ala Leu Arg Gln Lys
65                  70                  75                  80
Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp
                85                  90                  95
Val Leu Lys Glu Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu
            100                 105                 110
Leu Ser Val Glu Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Lys
        115                 120                 125
Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys
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Ala Val Asp His Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr
145                 150                 155                 160
Glu Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys
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Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe
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Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val
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Thr Val Thr Glu Ser Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys
            260                 265                 270
Cys Asp Leu Ala Pro Glu Ala Arg Gln Ala Ile Lys Ser Leu Thr Glu
        275                 280                 285
Arg Leu Tyr Ile Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys
    290                 295                 300
Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly
305                 310                 315                 320
Asn Thr Leu Thr Cys Tyr Leu Lys Ala Ser Ala Ala Cys Arg Ala Ala
                325                 330                 335
Lys Leu Gln Asp Cys Thr Met Leu Val Asn Gly Asp Asp Leu Val Val
            340                 345                 350
Ile Cys Glu Ser Ala Gly Thr Gln Glu Asp Ala Ala Asn Leu Arg Val
        355                 360                 365
Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Leu Pro
    370                 375                 380
Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val
385                 390                 395                 400
Ser Val Ala His Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg
                405                 410                 415
Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His
            420                 425                 430
Thr Pro Ile Asn Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr
        435                 440                 445
Leu Trp Ala Arg Met Val Leu Met Thr His Phe Phe Ser Ile Leu Leu
    450                 455                 460
Ala Gln Glu Gln Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala
465                 470                 475                 480
Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Gln Ile Ile Glu Arg Leu
                485                 490                 495
His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile
            500                 505                 510
Asn Arg Val Ala Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg
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Val Trp Arg His Arg Ala Arg Ser Val Arg Ala Lys Leu Leu Ser Gln
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Gly Gly Arg Ala Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val
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Arg Thr Lys Leu Lys Leu Thr Pro Ile Pro Ala Ala Ser Arg Leu Asp
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